HEPATITIS C VIRUS INHIBITORS

The present disclosure is generally directed to antiviral compounds, and more specifically directed to compounds which inhibit the function of the NS3 protease (also referred to herein as "serine protease") encoded by Hepatitis C virus (HCV), compositions comprising such compounds, and methods for inhibiting the function of the NS3 protease.

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.

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. Thus, there is a clear and unmet need to develop effective therapeutics for treatment of HCV infection.

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.

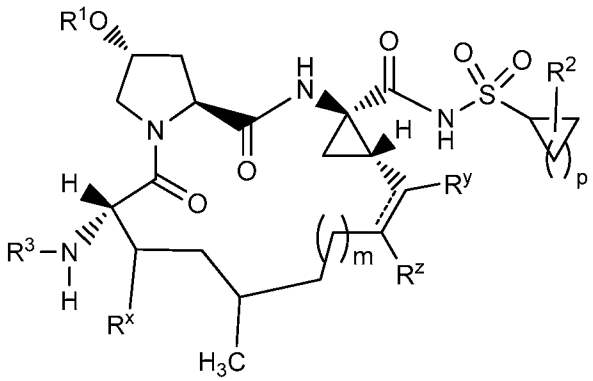
Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. Six major genotypes have been characterized, and more than 50 subtypes have been described. The major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the possible effect of genotypes on pathogenesis and therapy.

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 cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the *N*-terminal region of NS3 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 co-factor 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 is essential for efficient polyprotein processing, enhancing the proteolytic cleavage at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B is a RNA-dependent RNA polymerase that is involved in the replication of HCV.

The present disclosure provides peptide compounds that can inhibit the functioning of the NS3 protease, e.g., in combination with the NS4A protease. Further, the present disclosure describes the administration of combination therapy to a patient whereby a compound in accordance with the present disclosure, which is effective to inhibit the HCV NS3 protease, can be administered with additional compounds having anti-HCV activity.

In its first aspect the present disclosure provides a compound of formula (I)



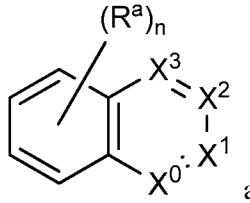
(I),

or a pharmaceutically acceptable salt thereof, wherein

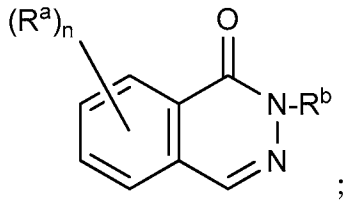
p is 1 or 2;

----- is a single or double bond;

R^1 is selected from



and



;

wherein R^1 is attached to the parent molecular moiety through any substitutable carbon atom in the group;

m is 0, 1, or 2;

n is 0, 1, 2, 3, 4, 5, or 6;

X^0 is selected from CH and N;

X^1 is selected from CH and N;

X^2 and X^3 are independently selected from CH, $C(R^a)$ and N; provided that at least one of X^1, X^2, and X^3 is other than N;

each R^a is independently selected from alkenyloxy, alkoxy, alkoxyalkoxy, alkyl, benzodioxanyl, carboxamido, carboxy, carboxyalkoxy, cyano, cycloalkylalkoxy, cycloalkyloxy, deuteroalkoxy, dialkylamino, halo, haloalkyl, haloalkoxy, haloalkoxycarbonyl, hydroxy, morpholinyl, phenyl, piperazinyl, pyrazolyl, and pyridinyl, pyrrolidinyl, wherein the morpholinyl, the phenyl, the piperazinyl, the pyridinyl, and the pyrrolidinyl are optionally substituted with one or two groups independently selected from alkoxy, alkyl, alkylsulfonyl, halo, haloalkoxy, haloalkyl, and morpholinyl; and wherein two adjacent R^a groups, together with the carbon atoms to which they are attached, can optionally form a ring selected from dioxanyl, dioxolanyl, morpholinyl, pyranyl, and phenyl, wherein the ring is optionally substituted with one or two groups independently selected from alkyl and halo;

R^b is alkyl;

R^x is selected from methyl and ethyl;

R^y and R^z are independently selected from hydrogen and hydroxy; provided that when ----- is a double bond, R^y and R^z are each hydrogen;

R^2 is selected from hydrogen, alkyl, halo, haloalkoxy, haloalkyl, and hydroxyalkyl; and

R^3 is selected from hydrogen, alkoxyalkoxycarbonyl, alkoxycarbonyl, alkylaminocarbonyl, alkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylcarbonyl, cycloalkyloxycarbonyl, deuteroalkoxycarbonyl, deuterohaloalkoxycarbonyl, dialkylaminocarbonyl, dialkylaminocarbonylcarbonyl, haloalkoxycarbonyl, haloalkylaminocarbonyl, haloalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, phenylcarbonyl, and phenyloxycarbonyl, wherein the cycloalkyl part of the cycloalkylalkoxycarbonyl, the cycloalkylcarbonyl, and the cycloalkyloxycarbonyl, the heterocyclyl part of the heterocyclylcarbonyl and the heterocyclyloxycarbonyl, and the phenyl part of the phenylcarbonyl and the phenyloxycarbonyl, is optionally substituted with one , two, or three groups independently selected from alkyl, alkylamino, alkylcarbonyl, cycloalkyl, dialkylamino, halo, haloalkoxy, and haloalkyl.

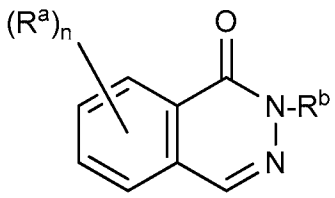
In a first embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein m is 1.

In a second embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein ----- is a double bond.

In a third embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein ----- is a double bond. In a fourth embodiment R^x is ethyl.

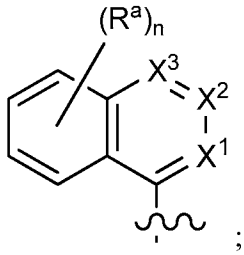
In a fifth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein ----- is a double bond and R^x is methyl.

In a sixth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is



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In a seventh embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is



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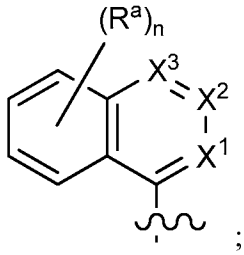
wherein X^1 and X^2 are N;

X^3 is $C(R^a)$;

n and R^a are as defined in claim 1; and

"〰" denotes the point of attachment to the parent molecular moiety.

In an eighth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is



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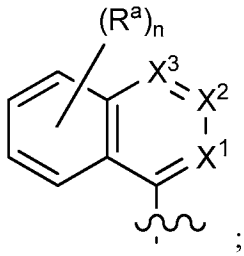
wherein X^1 is N;

X^2 and X^3 are independently selected from CH and $C(R^a)$;

n and R^a are as defined in claim 1; and

"〰" denotes the point of attachment to the parent molecular moiety.

In a ninth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is



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wherein X^1 and X^3 are N;

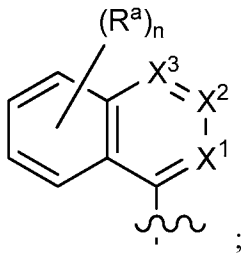
X^2 is $C(R^a)$;

n and R^a are as defined in claim 1; and

"〰" denotes the point of attachment to the parent molecular moiety.

In a tenth embodiment of the first aspect the present disclosure provides a

compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is



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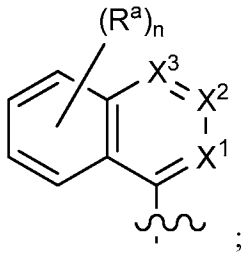
wherein X^1 and X^3 are N;

X^2 and X^3 are independently selected from CH and $C(R^a)$;

n and R^a are as defined in claim 1; and

"〰" denotes the point of attachment to the parent molecular moiety.

In an eleventh embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is



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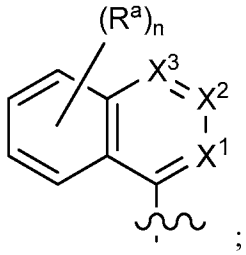
wherein X^1 and X^2 are independently selected from CH and $C(R^a)$;

X^3 is N;

n and R^a are as defined in claim 1; and

"〰" denotes the point of attachment to the parent molecular moiety.

In a twelfth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is



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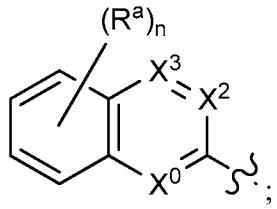
wherein X^1 and X^3 are N;

X^2 is CH;

n and R^a are as defined in claim 1; and

"〰" denotes the point of attachment to the parent molecular moiety.

In a thirteenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is



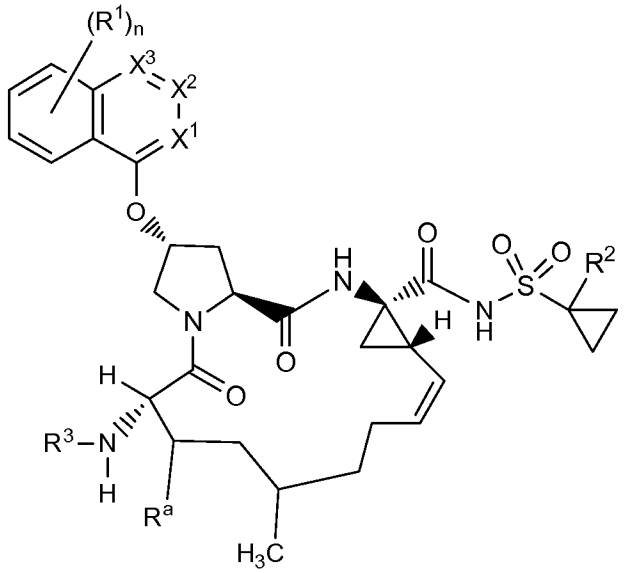
wherein X^0 and X^3 are N;

X^2 is selected from CH and $C(R^a)$;

n and R^a are as defined in claim 1; and

"〰" denotes the point of attachment to the parent molecular moiety.

In a second aspect the present disclosure provides a compound of formula (II)



(I),

or a pharmaceutically acceptable salt thereof, wherein

n is 0, 1, 2, 3, 4, 5, or 6;

X^1 is selected from CH and N;

X^2 and X^3 are independently selected from CH, $C(R^1)$ and N;

R^a is selected from methyl and ethyl;

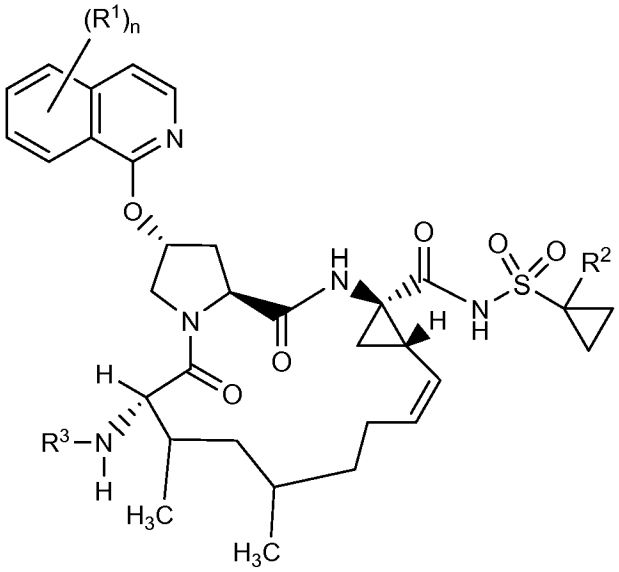
each R^1 is independently selected from alkoxy, alkyl, carboxamido, carboxy, cyano, cycloalkyloxy, dialkylamino, halo, haloalkyl, haloalkoxy, phenyl, and pyridinyl, wherein the phenyl and the pyridinyl are optionally substituted with one or

two groups independently selected from alkoxy, alkyl, halo, haloalkoxy, and haloalkyl;

R^2 is selected from hydrogen, alkyl, halo, and haloalkyl; and

R^3 is selected from alkoxycarbonyl, alkylcarbonyl, haloalkoxycarbonyl, haloalkylcarbonyl, and phenylcarbonyl, wherein the phenyl is optionally substituted with one or two groups independently selected from alkyl and halo.

In a third aspect the present disclosure provides a compound of formula (III)



(III),

or a pharmaceutically acceptable salt thereof, wherein

n is 0, 1, 2, 3, 4, 5, or 6;

each $R^1$is independently selected from alkoxy, alkyl, carboxamido, carboxy, cyano, cycloalkyloxy, dialkylamino, halo, haloalkyl, haloalkoxy, and phenyl, wherein the phenyl is optionally substituted with one or two groups independently selected from alkoxy, alkyl, halo, haloalkoxy, and haloalkyl;

R^2 is selected from hydrogen, alkyl, halo, and haloalkyl; and

R^3 is selected from alkoxycarbonyl, alkylcarbonyl, haloalkoxycarbonyl, haloalkylcarbonyl, and phenylcarbonyl, wherein the phenyl is optionally substituted with one or two groups independently selected from alkyl and halo;

or a pharmaceutically acceptable salt thereof.

In a fourth aspect the present disclosure provides a composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a

pharmaceutically acceptable carrier. In a first embodiment of the fourth aspect the present disclosure provides a composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, at least one additional compound having anti-HCV activity, and a pharmaceutical carrier. In a second embodiment at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau. In a fourth embodiment of the fourth aspect the present disclosure provides a composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, at least one additional compound having anti-HCV activity, and a pharmaceutical carrier, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, Imiquimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine. In a fifth embodiment of the fourth aspect the present disclosure provides a composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, at least one additional compound having anti-HCV activity, and a pharmaceutical carrier, wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

In a fifth aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof. In a first embodiment of the fifth aspect the method further comprises administering at least one additional compound having anti-HCV activity prior to, after, or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof. In a second embodiment of the fifth aspect at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau. In a fourth embodiment of the third aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically

acceptable salt thereof, and at least one additional compound having anti-HCV activity prior to, after, or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, Imiquimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine. In a fifth embodiment of the fifth aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional compound having anti-HCV activity prior to, after, or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

Other aspects of the present disclosure may include suitable combinations of embodiments disclosed herein.

Yet other aspects and embodiments may be found in the description provided herein.

The description of the present disclosure herein should be construed in congruity with the laws and principals of chemical bonding. In some instances it may be necessary to remove a hydrogen atom in order to accommodate a substitutent at any given location.

It should be understood that the compounds encompassed by the present disclosure are those that are suitably stable for use as pharmaceutical agent.

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. For example, when n is 2, each of the two R^1 groups may be the same or different.

All patents, patent applications, and literature references cited in the specification are herein incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

As used herein, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise.

The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to ten carbon atoms.

The term "alkylcarbonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "alkylsulfonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "carbonyl," as used herein, refers to -C(O)-.

The term "carboxamido," as used herein, refers to $-C(O)NR^xR^y$, wherein R^x and R^y are independently selected from hydrogen and alkyl.

The term "carboxy," as used herein, refers to $-CO_2H$.

The term "cyano," as used herein, refers to –CN.

The term "cycloalkyl," as used herein, refers to a saturated monocyclic or bicyclic hydrocarbon ring system having three to seven carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, and cyclopentyl.

The term "cycloalkyloxy," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "dialkylamino," as used herein, refers to $-NR^pR^q$, wherein R^p and R^q are alkyl groups. The alkyl groups may be the same or different.

The terms "halo" and "halogen," as used herein, refer to F, Cl, Br, and I.

The term "haloalkoxy," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "haloalkoxycarbonyl," as used herein, refers to a haloalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "haloalkyl," as used herein, refers to an alkyl group substituted with one, two, three, or four halogen atoms.

The term "haloalkylcarbonyl," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "phenylcarbonyl," as used herein, refers to a phenyl group attached to the parent molecular moiety through a carbonyl group.

The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, 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. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable basic functionality with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting an acidic group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, and *N,N'*-dibenzylethylenediamine. Other

representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

As used herein, the term "anti-HCV activity" means the compound is effective to treat the HCV virus.

The term "compounds of the disclosure", and equivalent expressions, are meant to embrace compounds of formula (I), and pharmaceutically acceptable enantiomers, diastereomers, and salts thereof. Similarly, references to intermediates, are meant to embrace their salts where the context so permits.

The term "patient" includes both human and other mammals.

The term "pharmaceutical composition" means a composition comprising a compound of the disclosure in combination with at least one additional pharmaceutical carrier, i.e., adjuvant, excipient or vehicle, such as diluents, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms. Ingredients listed in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Company, Easton, PA (1999) for example, may be used.

The phrase "pharmaceutically acceptable" is employed herein to refer 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 risk/benefit ratio.

The term "sulfonyl," as used herein, refers to -SO_2-.

The term "sulfoxyl," as used herein, refers to -S(O)-.

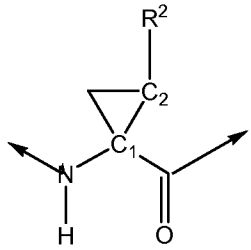
The term "therapeutically effective amount" means the total amount of each active component that is sufficient to show a meaningful patient benefit, e.g., a sustained reduction in viral load. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. 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 terms "treat" and "treating" refers to: (i) preventing a disease, disorder or

condition from occurring in a patient which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder or condition, i.e., arresting its development; and/or (iii) relieving the disease, disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

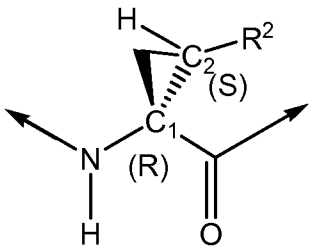
Where used in naming compounds of the present disclosure, the designations P1', P1, P2, P2*, P3, and P4, as used herein, map the relative positions of the amino acid residues of a protease inhibitor binding relative to the binding of the natural peptide cleavage substrate. Cleavage occurs in the natural substrate between P1 and P1' where the nonprime positions designate amino acids starting from the C-terminus end of the peptide natural cleavage site extending towards the *N*-terminus; whereas, the prime positions emanate from the *N*-terminus end of the cleavage site designation and extend toward the C-terminus. For example, P1' refers to the first position away from the right hand end of the C-terminus of the cleavage site (i.e. *N*-terminus first position); whereas P1 starts the numbering from the left hand side of the C-terminus cleavage site, P2: second position from the C-terminus, etc.). (see Berger A. & Schechter I., Transactions of the Royal Society London series (1970), B257, 249-264].

Asymmetric centers exist in the compounds of the present disclosure. For example, the compounds may include P1 cyclopropyl element of formula

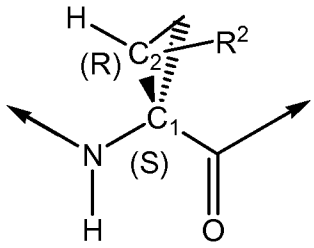


P1

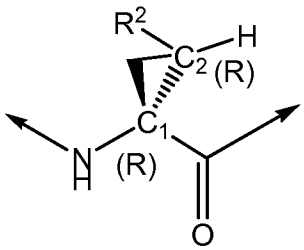
wherein C_1 and C_2 each represent an asymmetric carbon atom at positions 1 and 2 of the cyclopropyl ring.



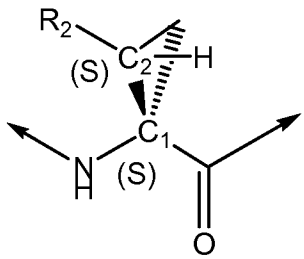
(1R, 2S)
R^2 is syn to carbonyl



(1S, 2R)
R^2 is syn to carbonyl



(1R, 2R)
R^2 is syn to amide



(1S, 2S)
R^2 is syn to amide

It should be understood that the disclosure encompasses all stereochemical forms, or mixtures thereof, which possess the ability to inhibit HCV protease.

Certain compounds of the present disclosure may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present disclosure includes each conformational isomer of these compounds and mixtures thereof.

Certain compounds of the present disclosure may exist in zwitterionic form and the present disclosure includes each zwitterionic form of these compounds and mixtures thereof.

When it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula (I), 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. Accordingly, the disclosure further

provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of formula (I) or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. 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 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.

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 150 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 disclosure are typical in a monotherapy 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. Generally, treatment is 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.

When the compositions of this disclosure comprise a combination of a compound of the disclosure and one or more additional therapeutic and/or

prophylactic agent, both the compound and the additional agent can be present in a dose that is less than or equal to the dosage normally administered in a monotherapy regimen. The compositions of this disclosure may be co-formulated with one or more additional therapeutic or prophylactic agents, for example, in the form of a monolithic and/or bi/multi-layer tablet or may be administered separately from the therapeutic or prophylactic agent(s).

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).

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

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.

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.

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 beta-lactose, corn sweeteners, natural and synthetic gums 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 diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelating, 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, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, 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.

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.

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 or embedding particulate material in polymers, wax, or the like.

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 phopholipids, such as cholesterol, stearylamine, or phophatidylcholines.

The compounds of formula (I) and pharmaceutically acceptable salts thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

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 Pharmaceutical Research, 3(6), 318 (1986).

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

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in oil base.

Pharmaceutical formulations adapted for topical administrations to the eye

include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles, and mouth washes.

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

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a course powder 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.

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, or insufflators.

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

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and soutes 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 a 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.

It should be understood that in addition to the 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.

Table 1 below lists some illustrative examples of compounds that can be administered with the compounds of this disclosure. The compounds of the

disclosure can be administered with other anti-HCV activity compounds in combination therapy, either jointly or separately, or by combining the compounds into a composition.

Table 1

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
NIM811		Cyclophilin Inhibitor	Novartis
Zadaxin		Immuno-modulator	Sciclone
Suvus		Methylene blue	Bioenvision
Actilon (CPG10101)		TLR9 agonist	Coley
Batabulin (T67)	Anticancer	β-tubulin inhibitor	Tularik Inc., South San Francisco, CA
ISIS 14803	Antiviral	antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	HCV Inhibitor	Achillion / Gilead
Pyrazolopyrimidine compounds and salts From WO-2005047288 26 May 2005	Antiviral	HCV Inhibitors	Arrow Therapeutics Ltd.
Levovirin	Antiviral	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
XTL-6865 (XTL-002)	Antiviral	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Isreal
Telaprevir (VX-950, LY-570310)	Antiviral	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN
HCV-796	Antiviral	NS5B Replicase Inhibitor	Wyeth / Viropharma
NM-283	Antiviral	NS5B Replicase Inhibitor	Idenix / Novartis
GL-59728	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
GL-60667	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
2'C MeA	Antiviral	NS5B Replicase Inhibitor	Gilead
PSI 6130	Antiviral	NS5B Replicase Inhibitor	Roche
R1626	Antiviral	NS5B Replicase Inhibitor	Roche
2'C Methyl adenosine	Antiviral	NS5B Replicase Inhibitor	Merck
JTK-003	Antiviral	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Levovirin	Antiviral	ribavirin	ICN Pharmaceuticals, Costa Mesa, CA
Ribavirin	Antiviral	ribavirin	Schering-Plough Corporation, Kenilworth, NJ

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Viramidine	Antiviral	Ribavirin Prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
SCH 503034	Antiviral	serine protease inhibitor	Schering Plough
Zadazim	Immune modulator	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Immunomodulator	immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
CellCept	Immunosuppressant	HCV IgG immuno-suppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Civacir	Immunosuppressant	HCV IgG immuno-suppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albuferon - α	Interferon	albumin IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferon	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferon	IFN-ω	Intarcia Therapeutics
IFN-β and EMZ701	Interferon	IFN-β and EMZ701	Transition Therapeutics Inc., Ontario, Canada

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Rebif	Interferon	IFN-β1a	Serono, Geneva, Switzerland
Roferon A	Interferon	IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Intron A	Interferon	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
Intron A and Zadaxin	Interferon	IFN-α2b/α1-thymosin	RegeneRx Biopharma. Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Rebetron	Interferon	IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Actimmune	Interferon	INF-γ	InterMune Inc., Brisbane, CA
Interferon-β	Interferon	Interferon-β-1a	Serono
Multiferon	Interferon	Long lasting IFN	Viragen/ Valentis
Wellferon	Interferon	Lympho-blastoid IFN-αn1	GlaxoSmithKline plc, Uxbridge, UK
Omniferon	Interferon	natural IFN-α	Viragen Inc., Plantation, FL
Pegasys	Interferon	PEGylated IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ceplene	Interferon	PEGylated IFN-α2a/ immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Pegasys and Ribavirin	Interferon	PEGylated IFN-α2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
PEG-Intron	Interferon	PEGylated IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	Interferon	PEGylated IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Liver protection	antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Liver protection	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	serine protease inhibitor	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	NS5B Replicase Inhibitor	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys
Boceprevir	Antiviral	serine protease inhibitor	Schering Plough
TMS-435	Antiviral	serine protease inhibitor	Tibotec BVBA, Mechelen, Belgium
BI-201335	Antiviral	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
MK-7009	Antiviral	serine protease inhibitor	Merck
PF-00868554	Antiviral	replicase inhibitor	Pfizer

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
ANA598	Antiviral	Non-Nucleoside NS5B Polymerase Inhibitor	Anadys Pharmaceuticals, Inc., San Diego, CA, USA
IDX375	Antiviral	Non-Nucleoside Replicase Inhibitor	Idenix Pharmaceuticals, Cambridge, MA, USA
BILB 1941	Antiviral	NS5B Polymerase Inhibitor	Boehringer Ingelheim Canada Ltd R&D, Laval, QC, Canada
PSI-7851	Antiviral	Nucleoside Polymerase Inhibitor	Pharmasset, Princeton, NJ, USA
PSI-7977	Antiviral	Nucleotide NS5B Polymerase Inhibitor	Pharmasset, Princeton, NJ, USA
VCH-759	Antiviral	NS5B Polymerase Inhibitor	ViroChem Pharma
INX-189	Antiviral	Nucleotide NS5B Polymerase Inhibitor	Inhibitex
VCH-916	Antiviral	NS5B Polymerase Inhibitor	ViroChem Pharma
GS-9190	Antiviral	NS5B Polymerase Inhibitor	Gilead
Peg-interferon lamda	Antiviral	Interferon	ZymoGenetics/Bristol-Myers Squibb

The compounds of the disclosure may also be used as laboratory reagents. Compounds may be instrumental in providing research tools for designing of viral replication assays, validation of animal assay systems and structural biology studies to further enhance knowledge of the HCV disease mechanisms. Further, the compounds of the present disclosure are useful in establishing or determining the binding site of other antiviral compounds, for example, by competitive inhibition.

The compounds of this disclosure may also be used to treat or prevent viral

contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials, e.g., blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection or transfusion apparatuses and materials.

This disclosure is intended to encompass compounds having formula (I) when prepared by synthetic processes or by metabolic processes including those occurring in the human or animal body (*in vivo*) or processes occurring *in vitro*.

The present disclosure will now be described in connection with certain embodiments which are not intended to limit its scope. On the contrary, the present disclosure covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include specific embodiments, will illustrate one practice of the present disclosure, it being understood that the examples are for the purposes of illustration of certain embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows: LAH for lithium aluminum hydride; THF for tetrahydrofuran; min for minutes; h or hr or hrs for hours; r.t. or RT or Rt for room temprature or retention time (context will dictate); MS for methanesulfonyl; DCM for dichloromethane; TBME for tert-butyl methyl ether; pet ether or pet-ether for petroleum ether; DMAP for N,N-dimethylaminpyridine; Ph for phenyl; LiHMDS for lithium hexamethyldisilazide; DIPEA or DIEA for diisopropylethylamine; $(BOC)_2O$ for di-tert-butyl dicarbonate; t-BuOK or tert-BuOK for potassium tert-butoxide; DMSO for N,N-dimethylsulfoxide; HATU for *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium phosphate; TFA for trifluoroacetic acid; EtOAC or EtOAc for ethyl acetate; DBU for 1,8-diazabicyclo(5.4.0)undec-7-ene; DMF for N,N-dimethylformamide; CDI for 1, 1'-carbonyldiimidazole; NH_4OAc for ammonium acetate; EtOH for ethanol; DDQ for 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DAST for (diethylamino) sulfur trifluoride; PPh_3 for triphenylphoshphine; TMS for trimethylsilane; and DPPA for diphenylphosphoryl azide.

The starting materials useful to synthesize the compounds of the present

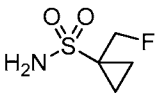
disclosure are known to those skilled in the art and can be readily manufactured or are commercially available.

The following methods set forth below are provided for illustrative purposes and are not intended to limit the scope of the claims. It will be recognized that it may be necessary to prepare such a compound in which a functional group is protected using a conventional protecting group then to remove the protecting group to provide a compound of the present disclosure. The details concerning the use of protecting groups in accordance with the present disclosure are known to those skilled in the art The preparation of intermediates and Compounds for Formula 1 is described in following three sections: Section1, Section 2 and Section 3. Compounds were named using ChemDraw.

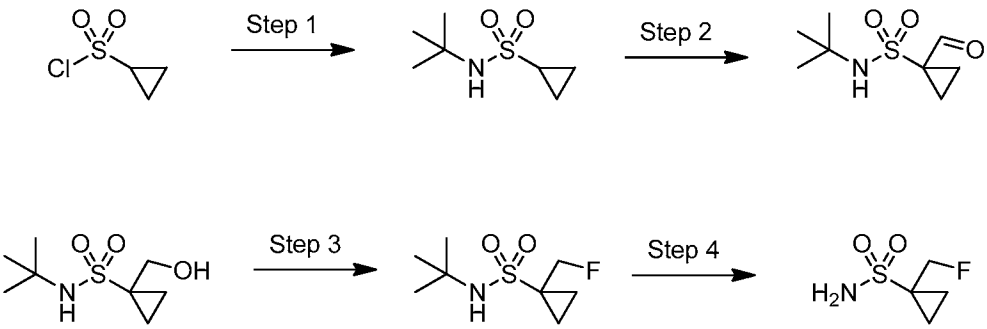
Preparation of Intermediates and Compounds of Formula 1:

Section 1:

Preparation of 1-(fluoromethyl)cyclopropane-1-sulfonamide



Scheme:



Step 1:

To a round-bottom flask equipped with a stir bar was added *tert*-butylamine (32.9 mL, 313 mmol) and dry THF (330 mL). The solution was cooled to -20 °C and to the stirred solution was added dropwise cyclopropanesulfonyl chloride (14.5 mL, 142 mmol). The solution was allowed to warm to room temperature with stirring for 18 h. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in DCM, washed with 1N HCl; water; and then brine. The organic solution was dried over $MgSO_4$, filtered, and then concentrated in vacuo. The resulting solid

was recrystallized from hexanes:EtOAc (5:1) to afford *N*-(*tert*-butyl)cyclopropanesulfonamide as a colorless crystalline solid (20.95 g, 83 %). ^{1}H NMR (400MHz, $CDCl_3$) δ 4.22 (br. s., 1H), 2.47 (tt, *J*=8.0, 4.9 Hz, 1H), 1.40 (s, 9H), 1.22 - 1.16 (m, 2H), 1.04 - 0.97 (m, 2H).

Step 2:

To a round-bottom flask equipped with a stir bar was added *N*-(*tert*-butyl)cyclopropanesulfonamide (10.0 g, 56.4 mmol) and THF (220 mL). The flask was placed under a nitrogen atmosphere and the solution was then cooled to -78 °C. To the stirred solution was added dropwise over 10 minutes *n*-butyllithium (46.3 mL, 2.5M in hexanes). The resulting solution was stired at -78 °C for 30 mins and then the cold bath was removed and the solution was allowed to warm to room temperature temperature with stirring for 30 mins. The solution was cooled to -78 °C. To the solution was added *N*,*N*-dimethylformamide (13.1 mL, 169 mmol). The solution was allowed to slowly warm to room temperature with stirring for 17 h. The mixture was concentrated and the resulting yellow residue was dissolved in EtOAc (100 mL). The solution was transferred to a separatory funnel and was washed with aq. 1N HCl (150 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL) and the combined organics were washed with sat. aq. NaCl (50 mL); dried over Na_2SO_4; and filtered. The filtrate concentrated in vacuo to afford a yellow viscous oil which solidified upon standing at room tempearture. This material was dissolved in EtOAc (10 mL); diluted with hexanes (50 mL); and the resulting solution was then stored at -78°C for 2 h upon which crystals formed. The crystals were collected via filtration; were washed with cold hexanes; and residual solvent was removed in vacuo to afford *N*-(*tert*-butyl)-1-formylcyclopropane-1-sulfonamide as a colorless, crystalline solid (8.89 g, 77%). ^{1}H NMR (500MHz, $CDCl_3$) δ 9.52 (s, 1H), 4.72 (br. s., 1H), 1.90 - 1.85 (m, 2H), 1.66 - 1.62 (m, 2H), 1.36 (s, 9H).

Step 3:

A round-bottom flask equipped with a stir bar was charged with a solution of *N*-(*tert*-butyl)-1-formylcyclopropane-1-sulfonamide (8.89 g, 43.3 mmol) in MeOH (110 mL). The solution was cooled to 0 °C and to the solution was added portionwise sodium borohydride (1.64 g, 43.3 mmol). The solution was stirred for 1 h. To the solution was added brine and the mixture was stirred for 15 min. The mixture was concentrated in vacuo to remove MeOH and the aqueous solution was then

transferred to separatory funnel and was twice extracted with EtOAc. The combined organics were washed with sat. aq. NaCl; dried over $MgSO_4$; filtered; and then concentrated in vacuo to afford *N*-(*tert*-butyl)-1-(hydroxymethyl)cyclopropane-1-sulfonamide as a colorless, crystalline solid (8.66 g, 96%). ^{1}H NMR (400MHz, $CDCl_3$) δ 4.35 (br. s., 1H), 3.86 (d, *J*=6.0 Hz, 2H), 2.77 (t, *J*=6.0 Hz, 1H), 1.50 - 1.45 (m, 2H), 1.39 (s, 9H), 1.06 - 1.01 (m, 2H).

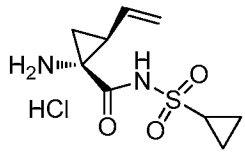
Step 4:

To a round-bottom flask equipped with a stir bar was added *N*-(*tert*-butyl)-1-(hydroxymethyl)cyclopropane-1-sulfonamide (8.66 g, 41.8 mmol) and CH_2Cl_2 (110 mL). The stirred solution was cooled to 0 °C and to the solution was added (diethylamino)sulfur trifluoride (11 mL, 84 mmol). The solution was allowed to warm to room temperature with stirring for 4 h. The solution was then slowly added to a stirred sat. aq. sodium bicarbonate (100mL) and following the addition stirring was maintained for 18 h. The pH of the aqueous phase was adjusted to pH=4 using aq. HCl. The mixture was transferred to a separatory funnel and was twice extracted with CH_2Cl_2. The combined organics were washed with brine; dried over $MgSO_4$; filtered; and then concentrated in vacuo to afford a brown solid residue. This material was subjected to SiO_2 chromatography (hexanes:EtOAc, 90:10 to 40:60) to afford *N*-(*tert*-butyl)-1-(fluoromethyl)cyclopropane-1-sulfonamide as a colorless, crystalline solid (5.66 g, 65%). ^{1}H NMR (400MHz, $CDCl_3$) δ 4.73 (s, 1H), 4.60 (s, 1H), 4.22 (br. s., 1H), 1.59 - 1.53 (m, 2H), 1.37 (s, 9H), 1.12 - 1.07 (m, 2H).

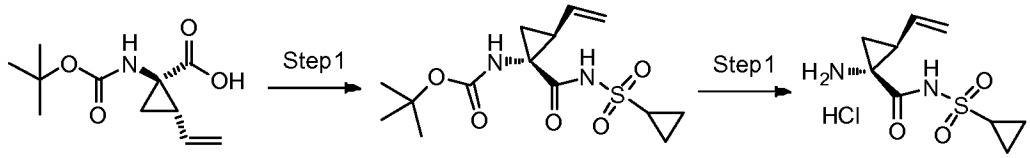
Step 5:

To a round-bottom flask equipped with a stir bar was added *N*-(*tert*-butyl)-1-(fluoromethyl)cyclopropane-1-sulfonamide (5.66 g, 27.0 mmol) and trifluoroacetic acid (20 mL). The solution was stirred at room temperature for 18 h. The solution was concentrated in vacuo to afford a dark orange oil. The oil was treated with hexanes:EtOAc (4:1) upon which a solid crystallized. The crystals were collected via filtrated and residual solvent was removed in vacuo to afford 1-(fluoromethyl)cyclopropane-1-sulfonamide as a colorless, crystalline solid (3.5 g, 84 %). ^{1}H NMR (400MHz, $CDCl_3$) δ 4.79 (s, 1H), 4.67 (s, 1H), 3.28 (br. s., 2H), 1.63 - 1.56 (m, 2H), 1.16 - 1.10 (m, 2H).

Preparation of (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide, HCl salt



Scheme



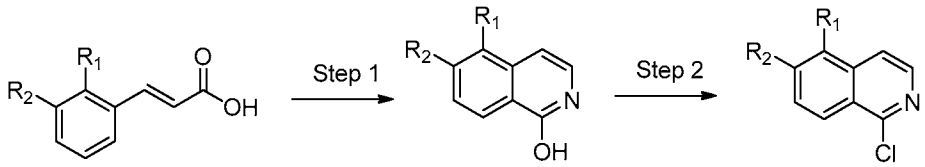
Step 1: tert-butyl ((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamate

A solution of (1R,2S)-1-((tert-butoxycarbonyl)amino)-2-vinylcyclopropanecarboxylic acid (2.62 g, 11.5 mmol) and CDI (2.43 g, 15.0 mmol) in THF (40 mL) was heated at reflux for 50 min under nitrogen. The solution was cooled to room temperature and transferred by cannula to a solution of cyclopropylsulfonamide (1.82 g, 15.0 mmol) in THF (10 mL). To the resulting solution was added DBU (2.40 mL, 16.1 mmol) and stirring was continued for 20 h. The mixture was quenched with 1N HCl to pH 1 and THF was evaporated in vacuo. The suspension was extracted with EtOAc (2 x 50 mL) and the combined organic extracts dried (Na2SO4). Purification by recystallization from hexanes-EtOAc (1:1) afforded the title compound (2.4 g) as a white solid. The mother liquor was purified by a Biotage 40S column (eluted 9% acetone in DCM) to give a second batch of the compound tert-butyl ((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamate (1.1 g). Both batches were combined (total yield 92%). ^{1}H NMR: (DMSO-d6) δ ppm 0.96-1.10 (m, 4H), 1.22 (dd, J=5.5, 9.5 Hz, 1H), 1.39 (s, 9H), 1.70 (t, J=5.5 Hz, 1H), 2.19-2.24 (m, 1H), 2.90 (m, 1H), 5.08 (d, J=10 Hz, 1H), 5.23 (d, J=17 Hz, 1H), 5.45 (m, 1H), 6.85, 7.22 (s, NH (rotamers) ; LC-MS MS m/z 331 (M^++H).

Step 2: (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide, HCl

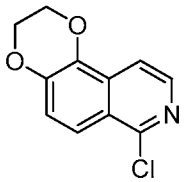
A solution of tert-butyl ((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamate (3.5 g, 10.6 mmol) in DCM (35 mL) and TFA (32 mL) was stirred at room temperature for 1.5 h. The volatiles were removed in vacuo and the residue suspended in 1N HCl in diethyl ether (20 mL) and concentrated in vacuo. This procedure was repeated once. The resulting mixture was triturated from pentane and filtered to give the compound (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide, HCl (2.60 g, 92%).^{1}H NMR: (DMSO-d6) δ ppm 1.01-1.15 (m, 4H), 1.69-1.73 (m, 1H), 1.99-2.02 (m, 1H), 2.38 (q, J=9 Hz, 1H), 2.92-2.97 (m, 1H), 5.20 (d, J=11 Hz, 1H), 5.33 (d, J=17 Hz, 1H), 5.52-5.59 (m, 1H), 9.17 (br s, 3H); LC-MS MS m/z 231 (M^++H).

General Synthetic Scheme



Preparation of P2 Intermediates:

Preparation of intermediate 7-chloro-2,3-dihydro-[1,4]dioxino[2,3-f]isoquinoline



Step 1:

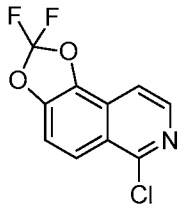
(E)-3-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)acrylic acid (5 g, 24.25 mmol), diphenylphosphoryl azide (4.96 mL, 23.04 mmol), and Et_3N (6.76 mL, 48.5 mmol) were dissolved in benzene and stirred for 16 h. The solution was concentrated under vacuum and the residue was purified by silica gel chromatography using 20% EtOAc/Hexanes to give 4.5 g of (E)-3-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)acryloyl azide as a yellow solid, which was taken into $PhCH_2Ph$ (50 mL). The resulting solution was slowly heated to 80°C for 1h and then to reflux for 3h. After cooling to

rt, the solid was collected washing with benzene to give 3.5 g of the desired product 2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-ol as a solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 4.37 (m, 4 H), 6.83 (d, *J*=7.09 Hz, 1 H), 7.02 (d, *J*=8.80 Hz, 1 H), 7.12 (d, *J*=7.34 Hz, 1 H), 7.79 (d, *J*=8.80 Hz, 1 H); MS: $(M+H)^+$ 204.

Step 2:

A solution of 2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-ol (5 g, 24.61 mmol) in $POCl_3$ (50 mL) was refluxed for 14 h. After Concentration, the residue was taken into the mixture of DCM and 4N NaOH solution. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using 20% EtOAc/Hexanes as eluent to give 4 g of the desired product 7-chloro-2,3-dihydro-[1,4]dioxino[2,3-f]isoquinoline as a solid. ^{1}H NMR (400 Hz, $CDCl_3$) δ ppm 4.42 (m, 4 H), 7.24 (d, *J*=9.05 Hz, 1 H), 7.77 (d, *J*=5.87 Hz, 1 H), 7.84 (d, *J*=9.05 Hz, 1 H), 8.18 (d, *J*=5.87 Hz, 1 H); MS: $(M+H)^+$ 222.

Preparation of intermediate 6-chloro-2,2-difluoro-[1,3]dioxolo[4,5-f]isoquinoline



The intermediate 6-chloro-2,2-difluoro-[1,3]dioxolo[4,5-f]isoquinoline was prepared by following above General Scheme except that 3-(2,2-difluoro-benzo[1,3]dioxol-4-yl)-acrylic acid was used instead in step 1.

Step 1:

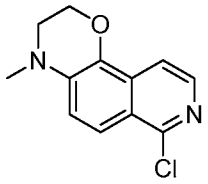
Modifications: 4.56 g 3-(2,2-difluoro-benzo[1,3]dioxol-4-yl)-acrylic acid used, 2.2 g product 2,2-difluoro-[1,3]dioxolo[4,5-f]isoquinolin-6(7H)-one was obtained (55% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.63 (d, *J*=7.09 Hz, 1 H), 7.29 (d, *J*=7.34 Hz, 1 H), 7.40 (d, *J*=8.80 Hz, 1 H), 8.19 (d, *J*=8.80 Hz, 1 H); MS: $(M+H)^+$ 226.

Step 2:

Modifications: 2.2 g 2,2-difluoro-7*H*-1,3-dioxa-7-aza-cyclopenta[a]naphthalen-6-one used, 2.1 g product 6-chloro-2,2-difluoro-

[1,3]dioxolo[4,5-f]isoquinoline obtained (87% yield). ^{1}H NMR (500 Hz, $CDCl_3$) δ ppm 7.51 (d, *J*=9.29 Hz, 1 H), 7.65 (d, *J*=5.87 Hz, 1 H), 8.22 (d, *J*=9.05 Hz, 1 H), 8.32 (d, *J*=5.87 Hz, 1 H); MS: $(M+H)^+$ 244.

Preparation of intermediate 7-chloro-4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinoline



The intermediate 7-chloro-4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinoline was prepared by following above General Scheme except that (E)-3-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)acrylic acid was used instead in step 1.

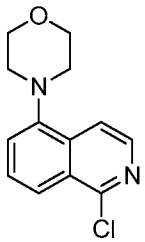
Step 1:

Modifications: 0.876 g (E)-3-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)acrylic acid used, 0.6 g product 4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-ol was obtained.

Step 2:

Modifications: 0.6 g 4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-ol used, 0.49 g product 7-chloro-4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinoline obtained. ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.05 (d, *J*=6.0 Hz, 1H), 7.82 (dd, *J*=9.3, 0.8 Hz, 1H), 7.67 (dd, *J*=5.8, 0.8 Hz, 1H), 7.16 (d, *J*=9.3 Hz, 1H), 4.47 - 4.36 (m, 2H), 3.48 - 3.41 (m, 2H), 3.06 (s, 3H); MS: $(M+H)^+$ 235.03.

Preparation of intermediate 4-(1-chloroisoquinolin-5-yl)morpholine



The intermediate 4-(1-chloroisoquinolin-5-yl)morpholine was prepared by following above General Synthetic Scheme except that (E)-3-(2-morpholinophenyl)acrylic acid was used instead in step 1.

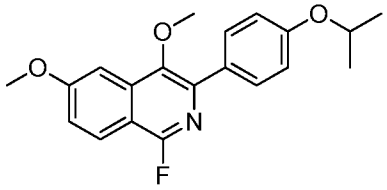
Step 1:

Modifications: 7 g (E)-3-(2-morpholinophenyl)acrylic acid used, 5 g 5-morpholinoisoquinolin-1-ol obtained (71% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 3.02 (m, 4 H), 3.91 (m, 4 H), 6.97 (d, *J*=7.34 Hz, 1 H), 7.18 (d, *J*=7.34 Hz, 1 H), 7.44 (m, 2 H), 8.02 (d, *J*=7.83 Hz, 1 H); MS $(M+H)^+$ 231.

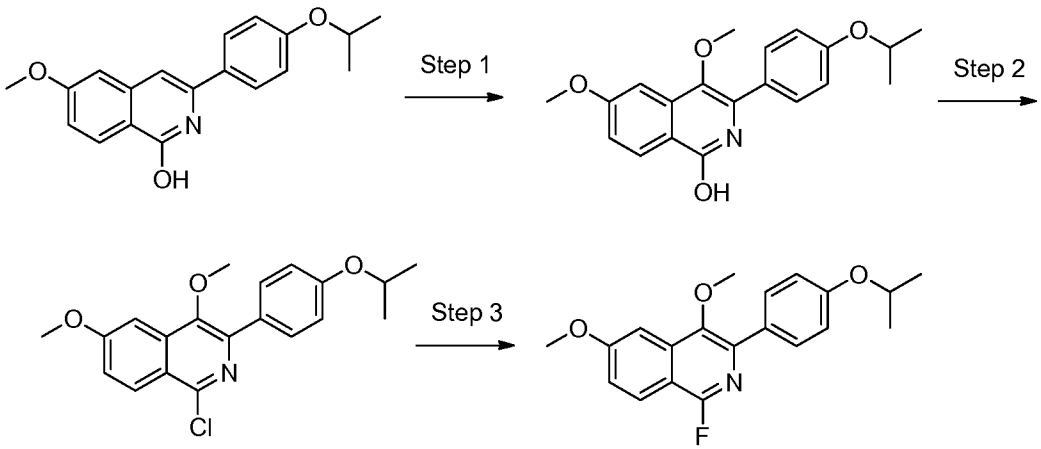
Step 2:

Modifications: 2.2 g 5-morpholin-4-yl-2*H*-isoquinolin-1-one used, 2.1 g 4-(1-chloroisoquinolin-5-yl)morpholine obtained (87% yield). ^{1}H NMR (400 MHz, CCl_3D) δ ppm 3.09 (m, 4 H), 3.97 (m, 4 H), 7.32 (d, *J*=7.58 Hz, 1 H), 7.60 (m, 1 H), 7.91 (d, *J*=5.87 Hz, 1 H), 8.06 (d, *J*=8.56 Hz, 1 H), 8.26 (d, *J*=5.87 Hz, 1 H).

Preparation of intermediate 1-fluoro-3-(4-isopropoxyphenyl)-4,6-dimethoxyisoquinoline



Scheme



Step 1:

In a 70 mL Chemglass pressure vessel were combined 3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-ol (1 g, 3.23 mmol), iodobenzene diacetate (1.145 g, 3.56 mmol) and MeOH (15 mL). To the mixture was added methanesulfonic acid (0.252 mL, 3.88 mmol), a mild exotherm resulted. The

threaded stopper was affixed to the vessel and the mixture was heated first to 70°C for 4 h and then to 130 °C for 3 h. Let the mixture stand at rt for 16 h. After filtration washing thoroughly with 1:1 methanol, the filtrate was extracted with ethyl acetate washing with water, dried over $MgSO_4$, concentrated to give an impure material that will be used in the next step as it is (1 g). MS: MS *m/z* 340.1 (M^++1).

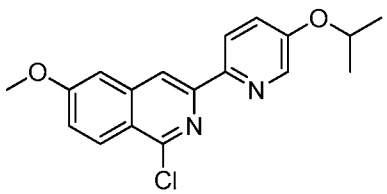
Step 2:

A solution of impure 3-(4-isopropoxyphenyl)-4,6-dimethoxyisoquinolin-1-ol (1 g, 2.95 mmol) in $POCl_3$ (10 mL) was refluxed for 1.5 hs. After concentration, the residue was taken into the mixture of DCM and 4N NaOH solution. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using 20% EtOAc/Hexanes as eluent to give 150 mg of the desired product. ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.14 (d, *J*=9.3 Hz, 1H), 8.08 (d, *J*=9.0 Hz, 2H), 7.39 (d, *J*=2.5 Hz, 1H), 7.22 (dd, *J*=9.3, 2.5 Hz, 1H), 7.01 (d, *J*=9.0 Hz, 2H), 4.65 (quin, *J*=6.1 Hz, 1H), 3.98 (s, 3H), 3.68 (s, 3H), 1.39 (d, *J*=6.0 Hz, 6H).

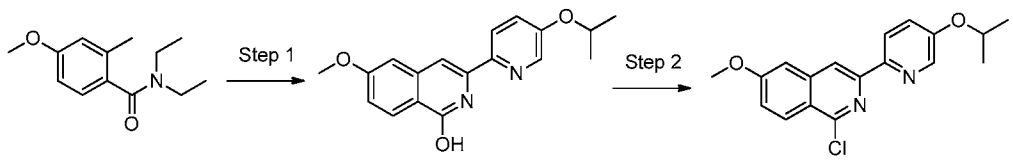
Step 3:

To a solution of 1-chloro-3-(4-isobutylphenyl)-4,6-dimethoxyisoquinoline (142 mg, 0.4 mmol) in DMSO (2 mL), was added CsF (122 mg, 0.800 mmol) and the mixture was heated to 140°C for 4 hrs. The reaction was diluted with ethylacteate and washed with water, and brine. The organic phase was collected, dried over sodium sulfate, and concentrated under vacuum to give the crude product which was purified by silica gel chromatography using a gradient of 5-25% EtOAc/Hexanes. The product fractions were collected and the solvent removed under vacuum to give 120 mg of the desired product as a white solid containing starting material. MS: MS *m/z* 342.1 (M^++1).

Preparation of intermediate 1-chloro-3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinoline



Scheme



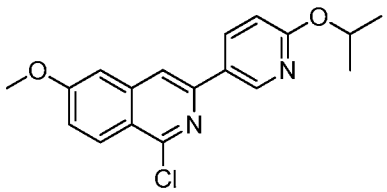
Step 1:

To a solution of N,N-diethyl-4-methoxy-2-methylbenzamide (4.43 g, 20 mmol) in THF (100 ml) at -78°C, tert-butyllithium 1.7 M in pentane (17.65 ml, 30.0 mmol) solution was added dropwise. The reaction mixture was stirred for 0.5 h before addition of 5-isopropoxypicolinonitrile (3.41 g, 21.00 mmol) in THF (2 mL). The resulting solution was warmed to rt and stirred for 16 h. The reaction mixture was quenched with water, neutralized with 1 N HCl. The precipitated solid (5 g) was collected and washed with water to give the product 3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-ol 4 g as a white solid. MS: MS *m/z* 311.11 (M^++1).

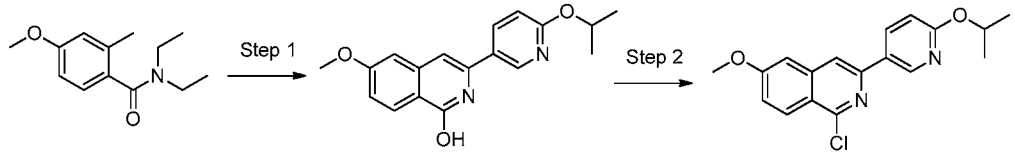
Step 2:

A solution of 3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-ol (4 g, 12.89 mmol) in $POCl_3$ (20 mL) was refluxed for 2 hs. After concentration, the residue was taken into the mixture of DCM and 4N NaOH solution. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using CH_2Cl_2 as eluent to give 3.4 g of the desired product 1-chloro-3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinoline as a solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.49 (s, 1H), 8.39 (d, *J*=8.8 Hz, 1H), 8.33 (d, *J*=2.5 Hz, 1H), 8.19 (d, *J*=9.1 Hz, 1H), 7.29 (dd, *J*=8.8, 3.0 Hz, 1H), 7.23 (dd, *J*=6.8, 2.5 Hz, 1H), 7.16 (d, *J*=2.3 Hz, 1H), 4.65 (spt, *J*=6.0 Hz, 1H), 3.94 (s, 3H), 1.38 (d, *J*=6.3 Hz, 6H).

Preparation of intermediate 1-chloro-3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinoline



Scheme



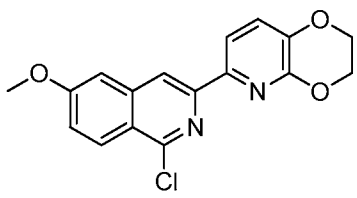
Step 1:

To a solution of N,N-diethyl-4-methoxy-2-methylbenzamide (1 g, 4.52 mmol) in THF (10 ml) at -78°C, tert-butyllithium 1.7 M, in pentane (3.19 ml, 5.42 mmol) was added dropwise. The reaction was stirred for 0.5 h before addition of 6-isopropoxynicotinonitrile (0.733 g, 4.52 mmol) in THF (2 mL). The resulting solution was warmed to rt and stirred for 16 h. The reaction mixture was quenched with water, neutralized with 1 N HCl. The precipitated solid (1.1 g) was collected and washed with water to give 500 mg of the product 3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-ol as a white solid. MS: MS *m/z* 311.11 (M^++1).

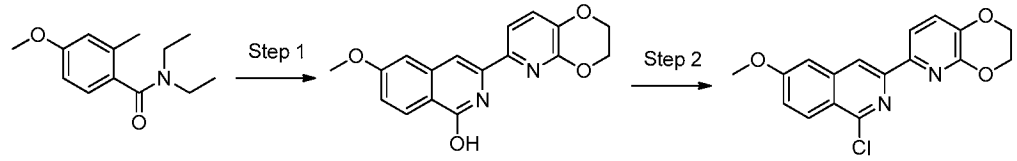
Step 2:

A solution of 3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-ol (400 mg, 1.289 mmol) in $POCl_3$ (5 mL, 53.6 mmol) was refluxed for 14 h. Concentrated the solvent. The residue was taken into a mixture of DCM and 4N NaOH solution. The solution was adjusted PH to 7. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using 10% EtOAc/Hexanes as eluent to give 289 mg of the desired product 1-chloro-3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinoline as a solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.83 (dd, *J*=2.6, 0.6 Hz, 1H), 8.32 (dd, *J*=8.5, 2.5 Hz, 1H), 8.22 (d, *J*=9.3 Hz, 1H), 7.82 (s, 1H), 7.253 (dd, *J*=6.8, 2.5 Hz, 1H), 7.13 (d, *J*=2.5 Hz, 1H), 6.81 (dd, *J*=8.7, 0.6 Hz, 1H), 5.40 (quin, *J*=6.1 Hz, 1H), 4.00 (s, 3H), 1.41 (d, *J*=6.0 Hz, 6H). MS: MS *m/z* 329.02 (M^++1).

Preparation of intermediate 1-chloro-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinoline



Scheme



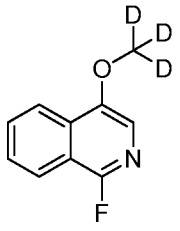
Step 1:

To a solution of N,N-diethyl-4-methoxy-2-methylbenzamide (100 mg, 0.452 mmol) in THF (10 ml) at -78°C, tert-butyllithium 1.7 M in pentane (0.319 ml, 0.542 mmol) was added dropwise. The solution was stirred for 0.5 h before addition of 2,3-dihydrobenzo[b][1,4]dioxine-6-carbonitrile (72.8 mg, 0.452 mmol) in THF (2 mL). The resulting solution was warmed to rt and stirred for 16 h. The reaction mixture was quenched with water, neutralized with 1 N HCl. The precipitated solid was collected and washed with water to give the product 3-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl)-6-methoxyisoquinolin-1-ol 120 mg as a solid after drying. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 8.07 (d, *J*=8.8 Hz, 1H), 7.31 (d, *J*=2.3 Hz, 1H), 7.27 (dd, *J*=8.3, 2.3 Hz, 1H), 7.14 (d, *J*=2.5 Hz, 1H), 7.02 (dd, *J*=8.8, 2.5 Hz, 1H), 6.96 (d, *J*=8.6 Hz, 1H), 6.77 (s, 1H), 4.29 (s, 4H), 3.87 (s, 3H).

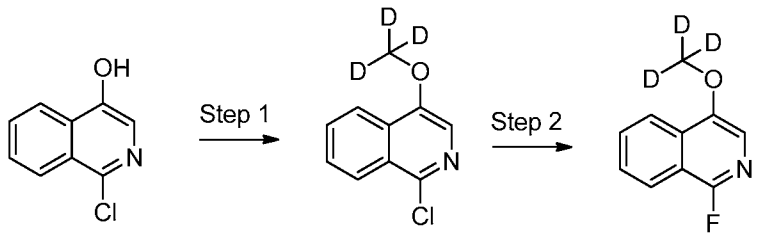
Step 2:

A solution of 3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinolin-1-ol (250 mg, 0.808 mmol) in $POCl_3$ (5 mL, 53.6 mmol) was refluxed for 14 h. Concentrated the solvent. The residue was taken into a mixture of DCM and 4N NaOH solution. Adjust pH to 7. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using 10% EtOAc/Hexanes as eluent to give 200 mg of the desired product 1-chloro-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinoline as a solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.18 (d, *J*=9.3 Hz, 1H), 7.77 (s, 1H), 7.65 - 7.55 (m, 2H), 7.21 (dd, *J*=9.2, 2.4 Hz, 1H), 7.08 (d, *J*=2.3 Hz, 1H), 6.95 (d, *J*=8.3 Hz, 1H), 4.30 (s, 4H), 3.95 (s, 3H).

Preparation of intermediate 1-fluoro-(4-D3-methoxy)isoquinoline



Scheme



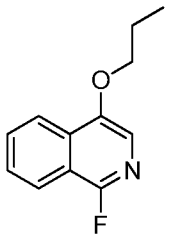
Step 1:

A mixture of 1-chloroisoquinolin-4-ol (898 mg, 5 mmol), CD_3I (1450 mg, 10.00 mmol), and K_2CO_3 (2073 mg, 15.00 mmol) in Acetone (20 mL) was refluxed for 16 h. After filtration, the solid was washed with acetone. The filtrate was concentrated and purified by silica gel chromatography eluting with 10-20% ethyl acetate in hexane to give 300 mg of 1-chloro-(4-D3-methoxy)isoquinoline. MS: MS *m/z* 197.1 (M^++1).

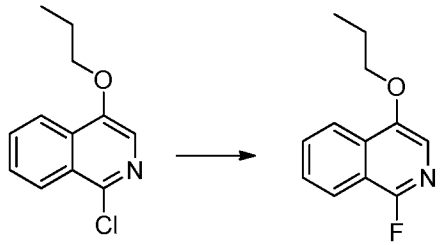
Step 2:

To a solution of 1-chloro-(4-D3-methoxy)isoquinoline (197 mg, 1 mmol) in DMSO (2 mL), added CsF (304 mg, 2.000 mmol) and the mixture was heated to 140 °C for 4 hrs. The reaction was diluted with ethylacteate and washed with water, and brine. The organic phase was collected, dried over sodium sulfate, and concentrated under vacuum to give the crude product which was purified by silica gel chromatography using a gradient of 5-25% EtOAc/Hexanes. The product fractions were collected and the solvent removed under vacuum to give 180 mg of 1-fluoro-(4-D3-methoxy)isoquinoline as a white solid.

Preparation of intermediate 1-fluoro-4-propoxyisoquinoline

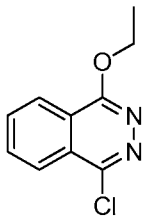


Scheme

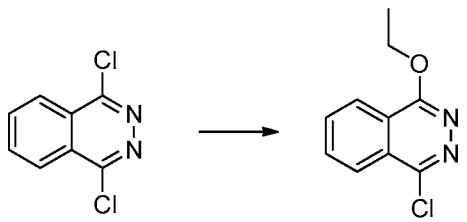


To a solution of 1-chloro-4-propoxyisoquinoline (1.1 g, 4.96 mmol) in DMSO (6 mL), added CsF (1.508 g, 9.92 mmol) and heated to 140 °C for 6 h. The reaction was diluted with ethylacteate and washed with water, and brine. The organic phase was collected, dried over sodium sulfate, and concentrated under vacuum to give the crude product which was purified by silica gel chromatography using a gradient of 5-25% EtOAc/Hexanes. The product fractions were collected and the solvent removed under vacuum to give 700 mg of the desired product 1-fluoro-4-propoxyisoquinoline as a white solid. MS: MS *m/z* 206.17 (M^++1).

Preparation of intermediate 1-chloro-4-ethoxyphthalazine

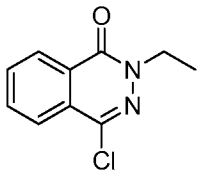


Scheme

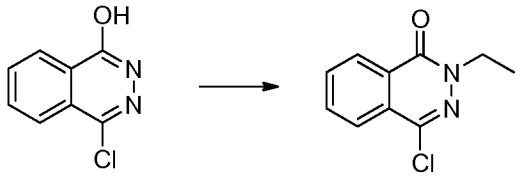


Sodium (33.8 mg, 1.470 mmol) was allowed to react with EtOH (10 mL), then 1,4-dichlorophthalazine (279 mg, 1.4 mmol) was added and the reaction mixture was refluxing for 30 min. The hot solution was filtered and evaporated. The crude product was purified by silica gel chromatography eluting with 20% ethyl acetate in hexane to give 200 mg of the crude product 1-chloro-4-ethoxyphthalazine. ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.29 - 8.18 (m, 2H), 7.99 - 7.90 (m, 2H), 4.73 (q, *J*=7.1 Hz, 2H), 1.57 (t, *J*=7.2 Hz, 3H); MS: MS *m/z* 209.06 (M^++1).

Preparation of intermediate 4-chloro-2-ethylphthalazin-1(2H)-one

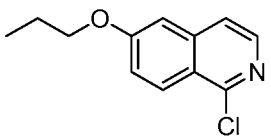


Scheme

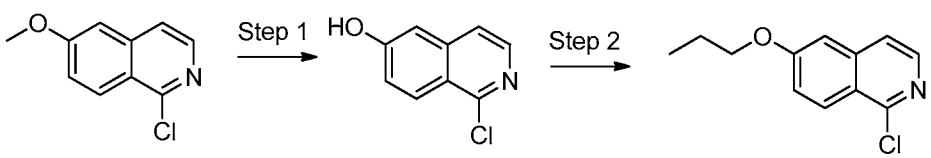


To a suspension of sodium hydride, 60% in mineral oil, (0.480 g, 12.00 mmol) in DMF (50 mL) was added 4-chlorophthalazin-1-ol (1.806 g, 10 mmol) at 0 °C. After stirring 30 min, the solution was transferred to a solution of iodoethane (2.339 g, 15.00 mmol) in DMF (50 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. The formed light yellow solid was filtered off and washed the cake with THF. The filtrate was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, concentrated to give a residue that was purified by silica gel chromatography eluting with 20% EtOAc in hexanes to afford 1.8 g of the desired product 4-chloro-2-ethylphthalazin-1(2H)-one as an oil. MS: MS *m/z* 209.06 (M^++1). ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.52 - 8.42 (m, 1H), 8.04 - 7.98 (m, 1H), 7.88 (dtd, *J*=18.5, 7.5, 1.5 Hz, 2H), 4.29 (q, *J*=7.1 Hz, 2H), 1.44 (t, *J*=7.2 Hz, 3H).

Preparation of intermediate 1-chloro-6-propoxyisoquinoline



Scheme



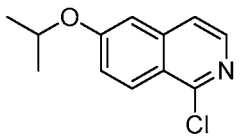
Step 1:

To a solution of 1-chloro-6-methoxyisoquinoline (1.93 g) in CH_2Cl_2 (30 mL) at -78 °C was added BBr_3 (30 mL, 30 mmol) via syringe. After warming to rt, the reaction mixture was stirred for 16 h. The reaction mixture was cooled to -78°C then quenched with 1 ml of MeOH. After concentration of the solvent, the residue was twice triturated with water to give 1.4 g of the desired product 1-chloroisoquinolin-6-ol as a solid. ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 8.26 (d, *J*=9.0 Hz, 1H), 8.16 (d, *J*=5.6 Hz, 1H), 7.43 (d, *J*=5.9 Hz, 1H), 7.27 (d, *J*=2.4 Hz, 1H), 7.12 (d, *J*=2.2 Hz, 1H).

Step 2:

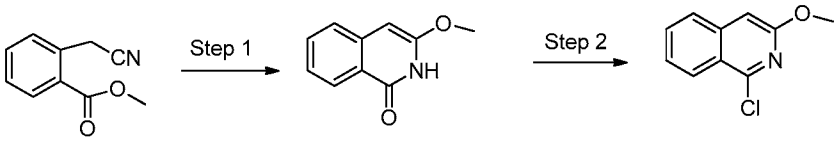
A mixture of 1-chloroisoquinolin-6-ol (0.898 g, 5 mmol), 1-bromopropane (1.230 g, 10.00 mmol), and K_2CO_3 (2.073 g, 15.00 mmol) in acetone (20 mL) was refluxed for 16 h. The reaction mixture was filtrated and washed with acetone. the filtrate was concentrated and purified by silica gel chromatography eluting with 10-20% ethyl acetate in hexane to give 700 mg of the product 1-chloro-6-propoxyisoquinoline as a solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.27 - 8.16 (m, 2H), 7.48 (d, *J*=5.8 Hz, 1H), 7.31 (dd, *J*=9.3, 2.5 Hz, 1H), 7.09 (d, *J*=2.5 Hz, 1H), 4.09 (t, *J*=6.5 Hz, 2H), 2.02 - 1.84 (m, 2H), 1.11 (d, *J*=14.8 Hz, 1H); MS: MS *m/z* 222.16 (M^++1).

Preparation of intermediate 1-chloro-6-isopropoxyisoquinoline



A mixture of 1-chloroisoquinolin-6-ol (898 mg, 5 mmol), 2-iodopropane (1700 mg, 10.00 mmol), and K_2CO_3 (2073 mg, 15.00 mmol) in acetone (20 mL) was refluxed for 16 h. The reaction mixture was filtrated and washed with acetone. the filtrate was concentrated and purified by silica gel chromatography eluting with 10-20% ethyl acetate in hexane to give 650 mg of the product 1-chloro-6-isopropoxyisoquinoline as a solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.30 - 8.13 (m, 2H), 7.47 (d, *J*=5.3 Hz, 1H), 7.27 (d, *J*=2.5 Hz, 1H), 7.09 (d, *J*=2.5 Hz, 1H), 4.77 (dt, *J*=12.2, 6.1 Hz, 1H), 1.45 (d, *J*=6.0 Hz, 6H); MS: MS *m/z* 222.16 (M^++1).

Preparation of 1-chloro-3-methoxyisoquinoline



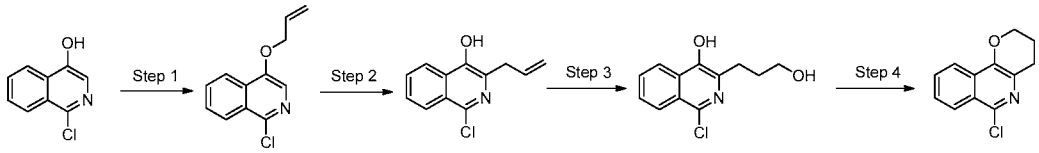
Step 1:

A mixture of methyl 2-(cyanomethyl)benzoate (3.50 g, 20 mmol) and sodium methoxide (10 mL, 25% wt in methanol) in 35 mL MeOH was heated to reflux under nitrogen for 3 h. While still hot, the solution was acidified with 1N HCl solution until the green solution turned to yellow color and a lot of white solid precipitated out. After cooling, the precipitated product was collected by filtration, washed with water and dried to yield the desired product 3-methoxyisoquinolin-1(2H)-one as a white solid (2.8 g, 80%). MS: MS *m/z* 176.1 (M^++1).

Step 2:

3-Methoxyisoquinolin-1(2H)-one (2.8 g, 16.0 mmol) in $POCl_3$ (10 mL) was heated to reflux for 3 h then evaporated *in vacuo.* The residue was poured into iced $NaHCO_3$ solution (50 mL). The product was extracted with EtOAc (2X). The organic layer was washed with brine, dried over $MgSO_4$, filtered, evaporated. The residue was purified by flash chromatography with 20% then 40% of EtOAc/ hexane to afford 1.36 g (44%) of the desired product 1-chloro-3-methoxyisoquinoline as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.29 - 8.16 (d, *J*=8.3 Hz, 1H), 7.72 (d, *J*=8.3 Hz, 1H), 7.63 (ddd, *J*=8.3, 6.8, 1.1 Hz, 1H), 7.47 (ddd, *J*=8.5, 7.0, 1.1 Hz, 1H), 6.98 (s, 1H), 4.05 (s, 3H). MS: MS *m/z* 194.0 (M^++1).

Preparation of 6-chloro-3,4-dihydro-2H-pyrano[3,2-c]isoquinoline



Step 1:

To a stirring solution of NaH (0.334 g, 8.35 mmol) in DMF (10 mL) at 0°C was added 1-chloroisoquinolin-4-ol (1 g, 5.57 mmol). The mixture was stirred at 0 °C for 10 min. before the addition of allyl bromide (0.808 g, 6.68 mmol) dropwise. The reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with ethyl acetate and then quenched with 1N HCl solution. The organic layer was washed with

brine, dried over $MgSO_4$, filtered and evaporated to get the crude material. The material was purified by flash chromatography with 20% of EtOAc/ hexane to afford 4-(allyloxy)-1-chloroisoquinoline (1.0 g, 4.55 mmol, 83 % yield) as a white solid. MS: MS *m/z* 220.1 (M^++1).

Step 2:

4-(allyloxy)-1-chloroisoquinoline (1.0 g, 4.55 mmol) was dissolved in diglyme (5 mL) and heated to 180 °C for 1 h. The reaction was cooled down to rt before adding EtOAc and water. Washed EtOAc layer with water then brine solution. The organic layer was then dried and concentrated. The residue was purified by flash chromatography with 20% of EtOAc/ hexane to afford 3-allyl-1-chloroisoquinolin-4-ol (670 mg, 67%) as product. MS: MS *m/z* 220.1 (M^++1).

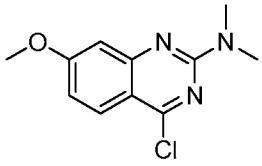
Step 3:

To a stirred solution of 3-allyl-1-chloroisoquinolin-4-ol (670 mg, 3.05 mmol) in dry tetrahydrofuran (5 mL) at room temperature was added 0.5 M in THF solution of 9-BBN (18.30 mL, 9.15 mmol) and the mixture was stirred for overnight. 3N NaOH (9.15 mL, 27.5 mmol) and H_2O_2 (2.83 mL, 30.5 mmol) were then added to the mixture. The mixture was stirred for 45 min before quenching with sat. NaCl solution. 1 N HCl was then added to the solution to adjust PH<7. The reaction was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated to afford a yellow oil that was purified by silica gel chromatography using 20-40%EtOAc/hexane to obtain 1-chloro-3-(3-hydroxypropyl)isoquinolin-4-ol (520mg , 70%) as product. MS: MS *m/z* 238.0 (M^++1).

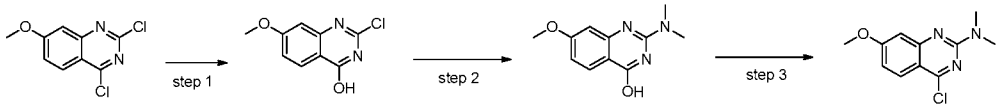
Step 4:

To a solution of triphenylphosphine (1.03 g, 3.94 mmol) and 1-chloro-3-(3-hydroxypropyl)isoquinolin-4-ol (520 mg, 2.18 mmol) in THF (2 mL) at 0 °C was added diisopropyl azodicarboxylate (0.85 mL, 4.38 mmol) dropwise. The resulting solution was stirred for 4 h at rt. After concentration of solvent, the residue was purified by silica gel chromatography eluting with 0%-20% ethyl acetate in hexane to give the desired product 6-chloro-3,4-dihydro-2H-pyrano[3,2-c]isoquinoline (350 mg, 73%) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.27 - 8.20 (m, 1H), 8.13 (d, *J*=8.3 Hz, 1H), 7.73 (ddd, *J*=8.2, 6.8, 1.3 Hz, 1H), 7.67 - 7.60 (m, 1H), 4.45 - 4.31 (m, 2H), 3.07 (t, *J*=6.5 Hz, 2H), 2.29 - 2.15 (m, 2H); MS: MS *m/z* 220.0 (M^++1).

Preparation of 4-chloro-7-methoxy-N,N-dimethylquinazolin-2-amine



Scheme



Step 1:

2,4-dichloro-7-methoxyquinazoline (500 mg, 2.183 mmol) was suspended in 2% aqueous NaOH (6 mL). THF (1 mL) was added and the reaction was stirred for 4 h. The reaction was diluted with water and the solid that remained was filtered off. The aqueous phase was diluted with 1 N HCl. The precipitate that formed was filtered, washed with water and dried to give 2-chloro-7-methoxyquinazolin-4-ol (288 mg, 63% yield). MS: MS *m/z* 211.1 (M^++1).

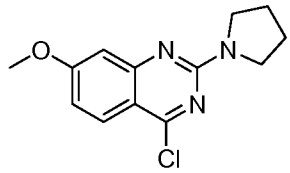
Step 2:

2-chloro-7-methoxyquinazolin-4-ol (288 mg, 1.368 mmol) was dissolved in Dimethylamine 2 M in THF (2 ml, 4.00 mmol) and heated to 100°C for 1 h in a sealed tube. The reaction was cooled and the volatiles were removed under vacuum. The crude solid was collected and washed with water, filtered and dried to give 2-(dimethylamino)-7-methoxyquinazolin-4-ol which was carried to the next step without further purification. MS: MS *m/z* 220.1 (M^++1).

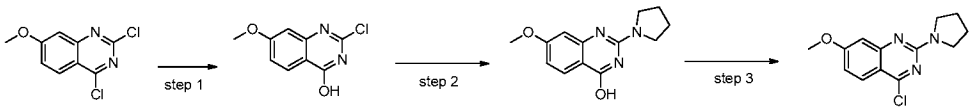
Step 3:

A solution of 2-(dimethylamino)-7-methoxyquinazolin-4-ol (300 mg, 1.368 mmol) in $POCl_3$ (2 ml, 21.46 mmol) was refluxed at 90 °C for 4 h. The reaction mixture was concentrated. The residue was dissolved in DCM and the pH was adjusted to 7 with 4N NaOH. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using DCM as eluent. The product fractions were collected and the solvent removed under vacuum to give 4-chloro-7-methoxy-2-(pyrrolidin-1-yl)quinazoline (325 mg, 100% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.29 (d, *J*=2.1 Hz, 1H), 7.97 (d, *J*=9.3 Hz, 1H), 7.07 (dd, *J*=9.2, 2.1 Hz, 1H), 4.08 (s, 3H), 3.71 (s, 3H), 3.49 (s, 3H); MS: MS *m/z* 238.0 (M^++1).

Preparation of 4-chloro-7-methoxy-2-(pyrrolidin-1-yl)quinazoline



Scheme



Step 1:

2,4-dichloro-7-methoxyquinazoline (500 mg, 2.183 mmol) was suspended in 2% aqueous NaOH (6 mL). THF (1 mL) was added and the reaction was stirred for 4 h. The reaction was diluted with water and the solid that remained was filtered off. The aqueous phase was diluted with 1 N HCl. The precipitate that formed was filtered, washed with water and dried to give 2-chloro-7-methoxyquinazolin-4-ol (288 mg, 63% yield). MS: MS *m/z* 211.1 (M^++1).

Step 2:

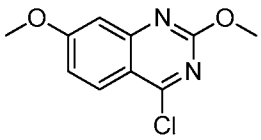
2-chloro-7-methoxyquinazolin-4-ol (165 mg, 0.783 mmol) and pyrolidine (0.130 mL, 1.567 mmol) were dissolved in THF (2 mL) and heated to 100°C for 2 h in a sealed tube. The reaction was cooled and the volatiles were removed under vacuum. The crude solid was collected and washed with water, filtered and dried to give 7-methoxy-2-(pyrrolidin-1-yl)quinazolin-4-ol which was carried to the next step without further purification. MS: MS *m/z* 246.2 (M^++1).

Step 3:

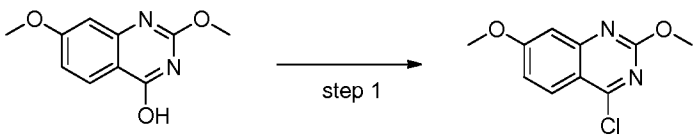
A solution of 7-methoxy-2-(pyrrolidin-1-yl)quinazolin-4-ol (155 mg, 0.632 mmol) in $POCl_3$ (2 ml, 21.46 mmol) was refluxed at 90 °C for 4 h. The reaction mixture was concentrated. The residue was dissolved in DCM and the pH was adjusted to 7 with 4N NaOH. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using 50% DCM in hexanes. The product fractions were collected and the solvent was removed under vacuum to give 4-chloro-7-methoxy-2-(pyrrolidin-1-yl)quinazoline (140 mg, 84% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 7.86 (d, *J*=9.0 Hz, 1H), 6.91 (d, *J*=2.3 Hz, 1H), 6.82 (dd,

J=9.0, 2.5 Hz, 1H), 3.92 (s, 3H), 3.69 (br. s., 4H), 2.03 (t, *J*=6.8 Hz, 4H); MS: MS *m/z* 264.1 (M^++1).

Preparation of 4-chloro-2,7-dimethoxyquinazoline



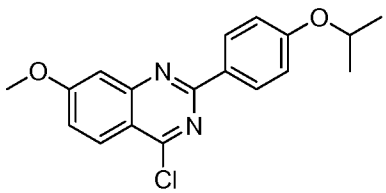
Scheme



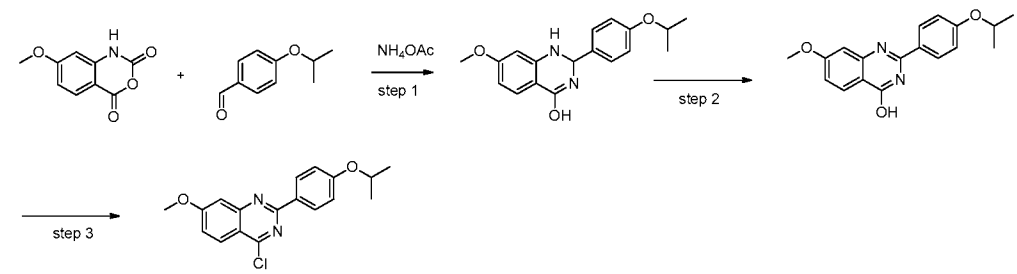
Step 1:

A solution of 2,7-dimethoxyquinazolin-4-ol (155 mg, 0.752 mmol) in $POCl_3$ (2 ml, 21.46 mmol) was refluxed for 4 h. The reaction mixture was concentrated. The residue was dissolved in DCM and the pH was adjusted to 7 with 4N NaOH. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using 50% DCM in hexanes. The product fractions were collected and the solvent removed under vacuum to give 4-chloro-2,7-dimethoxyquinazoline (61 mg, 36% yield). MS: MS *m/z* 225.1 (M^++1).

Preparation of 4-chloro-2-(4-isopropoxyphenyl)-7-methoxyquinazoline



Scheme



Step 1:

7-methoxy-1H-benzo[d][1,3]oxazine-2,4-dione (0.5 g, 2.59 mmol), 4-isopropoxybenzaldehyde (0.425 g, 2.59 mmol), and ammonium acetate (0.239 g, 3.11 mmol) were dissolved in EtOH (1 mL) and heated at 80 °C for 0.5 h. The solvent was removed under vacuum and the crude material was purified by silica gel chromatography using a gradient of 40-100% EtOAc in Hexanes. The product fractions were collected and concentrated under vacuum to give 2-(4-isopropoxyphenyl)-7-methoxy-1,2-dihydroquinazolin-4-ol (685 mg, 85% yield). MS: MS *m/z* 313.2 (M^++1).

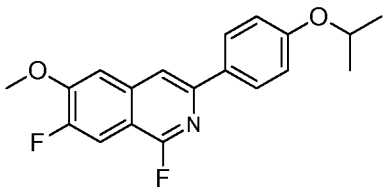
Step 2:

2-(4-isopropoxyphenyl)-7-methoxy-1,2-dihydroquinazolin-4-ol (685 mg, 2.193 mmol) was dissolved in DCM (10 mL) followed by the addition of DDQ (597 mg, 2.63 mmol). The reaction was stirred for 1 h. The reaction was diluted with DCM and filtered through celite. The filtrate was collected and concentrated under vacuum. The crude material was purified by silica gel chromatography using 40% EtOAc in hexanes. The product fractions were collected and the solvent removed under vacuum to give 2-(4-isopropoxyphenyl)-7-methoxyquinazolin-4-ol (495, 73% yield). MS: MS *m/z* 311.1 (M^++1).

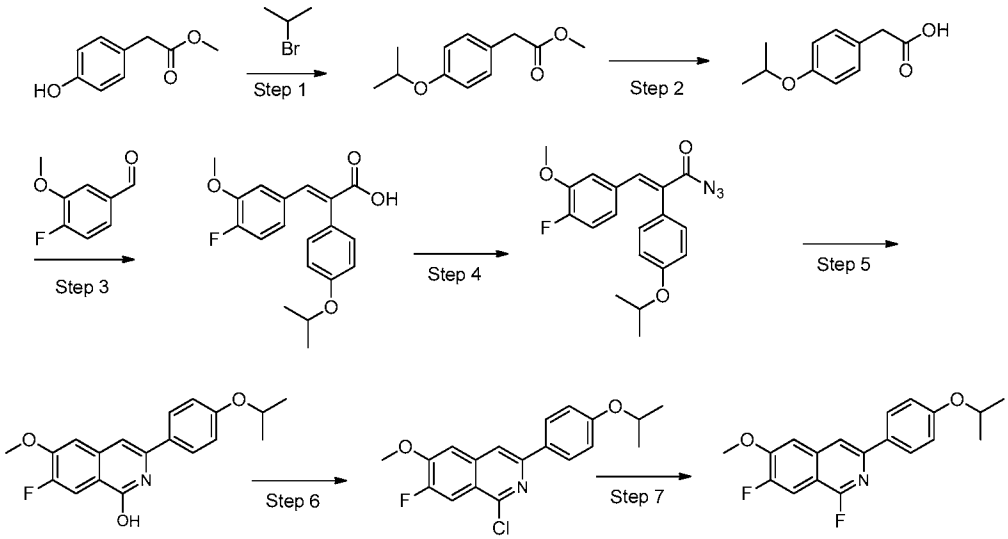
Step 3:

A solution of 2-(4-isopropoxyphenyl)-7-methoxyquinazolin-4-ol (495 mg, 1.595 mmol) in $POCl_3$ (2 ml, 21.46 mmol) was refluxed for 4 h. The reaction mixture was concentrated. The residue was dissolved in DCM and the pH was adjusted to 7 with 4N NaOH. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using 50% DCM in hexanes. The product fractions were collected and the solvent was removed under vacuum to give 4-chloro-2-(4-isopropoxyphenyl)-7-methoxyquinazoline (420 mg, 80% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.59 - 8.53 (m, 2H), 8.11 (d, *J*=9.3 Hz, 1H), 7.24 (dd, *J*=9.2, 2.4 Hz, 1H), 7.04 - 7.00 (m, 3H), 4.70 (quin, *J*=6.0 Hz, 1H), 4.03 (s, 3H), 1.40 (d, *J*=6.0 Hz, 6H); MS: MS *m/z* 329.1 (M^++1).

Preparation of 1,7-difluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinoline



Scheme



Step 1:

Methyl 2-(4-hydroxyphenyl)acetate (10 g, 60.2 mmol), 2-bromopropane (6.49 mL, 69.2 mmol), and potassium carbonate (8.32 g, 60.2 mmol) were heated to 50°C in DMF (100 mL) for overnight. The reaction was filtered and the organic layer was concentrated under vacuum. The crude material was purified by silica gel chromatography using a gradient of 0-20% EtOAc/hexanes. The product fractions were collected and the solvent removed under vacuum to give methyl 2-(4-isopropoxyphenyl)acetate (10 g, 80% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 7.22 - 7.14 (m, 2H), 6.88 - 6.82 (m, 2H), 4.53 (spt, *J*=6.1 Hz, 1H), 3.70 (s, 3H), 3.57 (s, 2H), 1.34 (d, *J*=6.0 Hz, 6H).

Step 2:

Methyl 2-(4-isopropoxyphenyl)acetate (10 g, 48.0 mmol), and NaOH (5.76 g, 144 mmol) were heated in methanol (50 mL)/Water (50 mL) solution at reflux for 2 h.

Most of the MeOH was removed under vacuum and the remaining aqueous solution was acidified with 1 N HCl. The solid that precipitated from the solution was extracted into EtOAc solution. The organic layer was collected, dried over sodium sulfate, and concentrated under vacuum to give 2-(4-isopropoxyphenyl)acetic acid (8.9 g, 95% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 7.22 - 7.16 (m, 2H), 6.88 - 6.83 (m, 2H), 4.53 (spt, *J*=6.1 Hz, 1H), 3.59 (s, 2H), 1.34 (d, *J*=6.0 Hz, 6H).

Step 3:

2-(4-isopropoxyphenyl)acetic acid (3.97 g, 20.44 mmol), 4-fluoro-3-methoxybenzaldehyde (3.15 g, 20.44 mmol), Ac2O (3.47 ml, 36.8 mmol), and Et3N (1.994 ml, 14.31 mmol) were heated to 110°C for 16 h. The reaction was cooled down to rt and diluted with water and EtOAc. The organic layer was collected, dried over sodium sulfate, and concentrated under vacuum. The crude material was purified by silica gel chromatography using 10-20% EtOAc/Hexanes. The product fractions were collected and the solvent removed under vacuum to give (E)-3-(4-fluoro-3-methoxyphenyl)-2-(4-isopropoxyphenyl)acrylic acid (4.4 g, 65% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 7.85 (s, 1H), 7.22 - 7.16 (m, 2H), 6.98 - 6.91 (m, 3H), 6.82 (ddd, *J*=8.3, 4.6, 2.1 Hz, 1H), 6.63 (dd, *J*=8.5, 2.0 Hz, 1H), 4.64 - 4.54 (m, 1H), 3.51 (s, 3H), 1.39 - 1.35 (m, 6H).

Step 4:

(E)-3-(4-fluoro-3-methoxyphenyl)-2-(4-isopropoxyphenyl)acrylic acid (4.38 g, 13.26 mmol), $(PhO)_2PON_3$ (2.71 mL, 12.60 mmol), and Et3N (3.70 mL, 26.5 mmol) were dissolved in benzene and stirred for 16 h. The solution was concentrated under vacuum and the residue was purified by silica gel chromatography using 20% EtOAc/Hexanes to give (E)-3-(4-fluoro-3-methoxyphenyl)-2-(4-isopropoxyphenyl)acryloyl azide (2.3 g, 49% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 7.80 (s, 1H), 7.16 - 7.11 (m, 2H), 6.97 - 6.92 (m, 2H), 6.84 - 6.78 (m, 1H), 6.63 - 6.53 (m, 2H), 4.63 - 4.54 (m, 1H), 3.49 (s, 3H), 1.38 - 1.35 (m, 6H).

Step 5:

A mixture of (E)-3-(4-fluoro-3-methoxyphenyl)-2-(4-isopropoxyphenyl)acryloyl azide (2.3 g, 6.47 mmol) in $PhCH_2Ph$ (30 ml) was slowly

heated to 80°C for 1 h and then to reflux for 3 h. After cooling to rt, the solid was collected, washed with benzene and dried under vacuum to give 7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-ol (383 mg, 20% yield). ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 7.83 (d, *J*=11.8 Hz, 1H), 7.70 (d, *J*=8.8 Hz, 2H), 7.40 (d, *J*=8.3 Hz, 1H), 7.03 (d, *J*=8.8 Hz, 2H), 6.82 (s, 1H), 4.72 (quin, *J*=6.0 Hz, 1H), 3.98 (s, 3H), 1.31 (d, *J*=6.0 Hz, 6H).

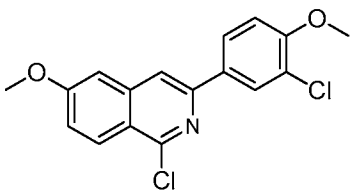
Step 6:

A solution of 7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-ol (1.8 g, 5.50 mmol) in $POCl_3$ (7.69 ml, 82 mmol) was refluxed for 4 h. The reaction mixture was concentrated. The residue was dissolved in DCM and the pH was adjusted to 7 with 4N NaOH. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using 50% DCM in hexanes. The product fractions were collected and the solvent removed under vacuum to give 1-chloro-7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinoline (1.8 g, 95% yield). MS: MS *m/z* 346.1 (M^++1).

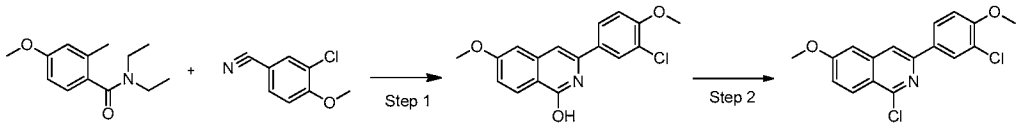
Step 7:

To a solution of 1-chloro-7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinoline (1 g, 2.89 mmol) in DMSO (6 mL), was added CsF (0.879 g, 5.78 mmol) and the mixture was heated to 140 °C for 4 hrs. The reaction was diluted with Ethylacteate and washed with water, and brine. The organic phase was collected, dried over sodium sulfate, and concentrated under vacuum to give the crude product which was purified by silica gel chromatography using 50% DCM/Hexanes. The product fractions were collected and the solvent removed under vacuum to give 1,7-difluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinoline (750 mg, 79% yield). MS: MS *m/z* 330.1 (M^++1).

Preparation of 1-chloro-3-(3-chloro-4-methoxyphenyl)-6-methoxyisoquinoline



Scheme



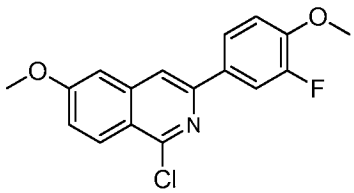
Step 1:

To a solution of N,N-diethyl-4-methoxy-2-methylbenzamide (1 g, 4.52 mmol) in THF (9 ml) at -78°C was added dropwise tert-butyllithium 1.7 M in pentane (3.19 ml, 5.42 mmol) and the solution was stirred for 0.5 h before addition of 3-chloro-4-methoxybenzonitrile (0.757 g, 4.52 mmol) in THF (9 ml). The resulting solution was warmed to rt and stirred for 16 h. The reaction mixture was quenched with water, neutralized with 1 N HCl. The precipitated solid was collected and washed with water to give 3-(3-chloro-4-methoxyphenyl)-6-methoxyisoquinolin-1-ol (1.2 g, 84% yield) as a solid after drying. MS: MS *m/z* 316.1 (M^++1).

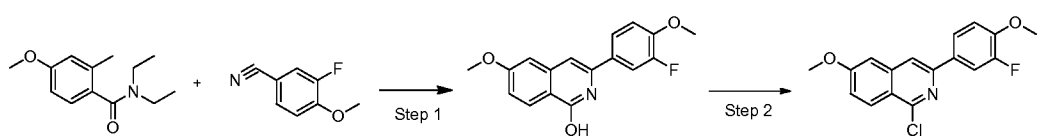
Step 2:

A solution of 3-(3-chloro-4-methoxyphenyl)-6-methoxyisoquinolin-1-ol (1.2 g, 3.80 mmol) in $POCl_3$ (5.31 ml, 57.0 mmol) was refluxed for 4 h. The reaction mixture was concentrated. The residue was dissolved in DCM and the pH was adjusted to 7 with 4N NaOH. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum to give 1-chloro-3-(3-chloro-4-methoxyphenyl)-6-methoxyisoquinoline (1.2 g, 95% yield). δ ppm ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.22 (d, *J*=9.3 Hz, 1H), 8.15 (d, *J*=2.3 Hz, 1H), 8.02 (dd, *J*=8.7, 2.4 Hz, 1H), 7.27 - 7.24 (m, 1H), 7.13 (d, *J*=2.5 Hz, 1H), 7.05 (d, *J*=8.5 Hz, 1H), 3.99 (s, 6H); MS: MS *m/z* 334.1 (M^++1).

Preparation of 1-chloro-3-(3-fluoro-4-methoxyphenyl)-6-methoxyisoquinoline



Scheme



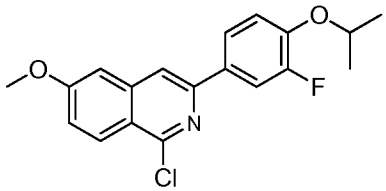
Step 1:

To a solution of N,N-diethyl-4-methoxy-2-methylbenzamide (1.00 g, 4.52 mmol) in THF (9 ml) at -78°C was added dropwise tert-butyllithium 1.7 M in pentane (3.19 ml, 5.42 mmol) and the solution was stirred for 0.5 h before addition of 3-fluoro-4-methoxybenzonitrile (0.683 g, 4.52 mmol) in THF (9 ml). The resulting solution was warmed to rt and stirred for 16 h. The reaction mixture was quenched with water, neutralized with 1 N HCl. The precipitated solid was collected and washed with water to give 3-(3-fluoro-4-methoxyphenyl)-6-methoxyisoquinolin-1-ol (926 mg, 69% yield) as a solid after drying. MS: MS *m/z* 300.1 (M^++1).

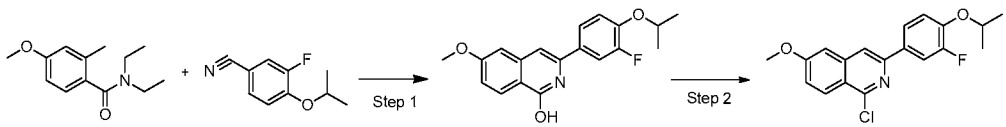
Step 2:

A solution of 3-(3-fluoro-4-methoxyphenyl)-6-methoxyisoquinolin-1-ol (1.2 g, 4.01 mmol) in $POCl_3$ (5.61 ml, 60.1 mmol) was refluxed for 4 h. The reaction mixture was concentrated. The residue was dissolved in DCM and the pH was adjusted to 7 with 4N NaOH. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum to give 1-chloro-3-(3-fluoro-4-methoxyphenyl)-6-methoxyisoquinoline (933 mg, 95% yield). δ ppm ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.21 (d, *J*=9.3 Hz, 1H), 7.90 - 7.87 (m, 1H), 7.86 (s, 1H), 7.81 (s, 1H), 7.27 - 7.23 (m, 1H), 7.12 (d, *J*=2.3 Hz, 1H), 7.10 - 7.04 (m, 1H), 3.98 (d, *J*=6.0 Hz, 6H); MS: MS *m/z* 318.1 (M^++1).

Preparation of 1-chloro-3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinoline



Scheme



Step 1:

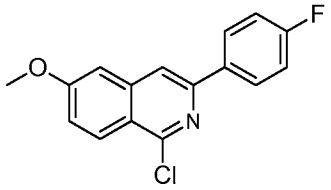
To a solution of N,N-diethyl-4-methoxy-2-methylbenzamide (500 mg, 2.259 mmol) in THF (5 ml) at -78°C was added dropwise tert-butyllithium 1.7 M in pentane (1595 µl, 2.71 mmol) and the solution was stirred for 0.5 h before addition of 3-

fluoro-4-isopropoxybenzonitrile (405 mg, 2.259 mmol) in THF (5 ml). The resulting solution was warmed to rt and stirred for 16 h. The reaction mixture was quenched with water, neutralized with 1 N HCl. The precipitated solid was collected washing with water to give 3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-ol (520 mg, 70% yield) as a solid after drying. MS: MS *m/z* 328.1 (M^++1).

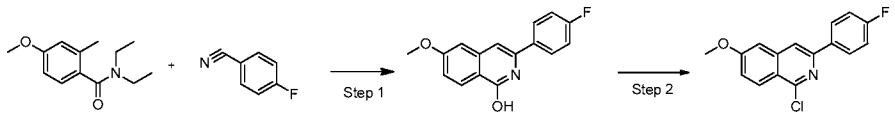
Step 2:

A solution of 3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-ol (700 mg, 2.138 mmol) in $POCl_3$ (2990 µl, 32.1 mmol) was refluxed for 4 h. The reaction mixture was concentrated. The residue was dissolved in DCM and the pH was adjusted to 7 with 4N NaOH. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using 50% DCM in hexanes as eluent. The product fractions were collected and the solvent removed under vacuum to give 1-chloro-3-(4-fluorophenyl)-6-methoxyisoquinoline (665 mg, 90% yield). MS: MS *m/z* 346.1 (M^++1).

Preparation of 1-chloro-3-(4-fluorophenyl)-6-methoxyisoquinoline



Scheme



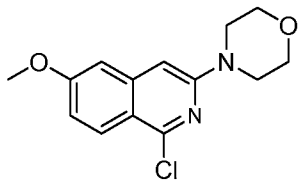
Step 1:

To a solution of N,N-diethyl-4-methoxy-2-methylbenzamide (500 mg, 2.259 mmol) in THF (4.52 ml) at -78°C was added dropwise tert-butyllithium 1.7 M in pentane (1.59 ml, 2.71 mmol) and the solution was stirred for 0.5 h before addition of 4-fluorobenzonitrile (274 mg, 2.259 mmol) in THF (4.52 ml). The resulting solution was warmed to RT and stirred for 16 h. The reaction mixture was quenched with water, neutralized with 1 N HCl. The precipitated solid was collected and washed with water to give 3-(4-fluorophenyl)-6-methoxyisoquinolin-1-ol (350 mg, 58% yield) as a solid after drying.

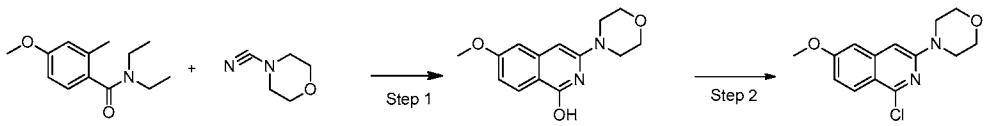
Step 2:

A solution of 3-(4-fluorophenyl)-6-methoxyisoquinolin-1-ol (350 mg, 1.300 mmol) in $POCl_3$ (1.82 ml, 19.50 mmol) was refluxed (90 °C) for 4 h. The reaction mixture was concentrated. The residue was dissolved in DCM and the pH was adjusted to 7 with 4N NaOH. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using 50% DCM in Hexanes as eluent. The product fractions were collected and the solvent removed under vacuum to give 1-chloro-3-(4-fluorophenyl)-6-methoxyisoquinoline (340 mg, 91% yield). MS: MS *m/z* 288.1 (M^++1).

Preparation of 4-(1-chloro-6-methoxyisoquinolin-3-yl)morpholine



Scheme



Step 1:

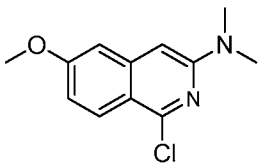
To a solution of N,N-diethyl-4-methoxy-2-methylbenzamide (500 mg, 2.259 mmol) in THF (5 ml) at -78°C was added dropwise tert-butyllithium 1.7 M in pentane (2658 µl, 4.52 mmol) and the solution was stirred for 0.5 h before addition of morpholine-4-carbonitrile (253 mg, 2.259 mmol) in THF (5 ml). The resulting solution was warmed to rt and stirred for 16 h. The reaction mixture was quenched with water, neutralized with 1 N HCl. The precipitated solid was collected and washed with water to give 6-methoxy-3-morpholinoisoquinolin-1-ol (350 mg, 60% yield) as a solid after drying.

Step 2:

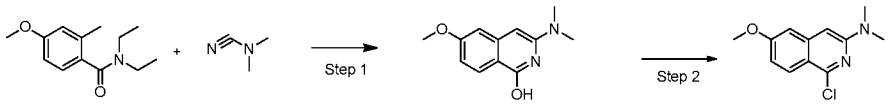
A solution of 6-methoxy-3-morpholinoisoquinolin-1-ol (315 mg, 1.210 mmol) in $POCl_3$ (1692 µl, 18.15 mmol) was refluxed for 4 h. The reaction mixture was concentrated. The residue was dissolved in DCM and the pH was adjusted to 7 with 4N NaOH. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel

chromatography using 50% DCM in Hexanes as eluent. The product fractions were collected and the solvent removed under vacuum to give 4-(1-chloro-6-methoxyisoquinolin-3-yl)morpholine (323 mg, 95% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.01 (d, *J*=9.3 Hz, 1H), 6.97 (dd, *J*=9.3, 2.5 Hz, 1H), 6.86 (d, *J*=2.5 Hz, 1H), 6.59 (s, 1H), 3.92 (s, 3H), 3.90 - 3.85 (m, 4H), 3.56 - 3.50 (m, 4H); MS: MS *m/z* 279.1 (M^++1).

Preparation of 1-chloro-6-methoxy-N,N-dimethylisoquinolin-3-amine



Scheme



Step 1:

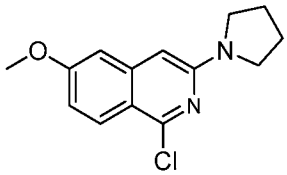
To a solution of N,N-diethyl-4-methoxy-2-methylbenzamide (1000 mg, 4.52 mmol) in THF (10 ml) at -78°C was added dropwise tert-butyllithium 1.7 M in pentane (5316 µl, 9.04 mmol) and the solution was stirred for 0.5 h before addition of N,N-dimethylcyanamide (317 mg, 4.52 mmol) in THF (10 ml). The resulting solution was warmed to rt and stirred for 16 h. The reaction mixture was quenched with water, neutralized with 1 N HCl, and extracted with EtOAc. The organic layer was collected, dried over sodium sulfate, filtered, followed by removal of solvent under vacuum to give 3-(dimethylamino)-6-methoxyisoquinolin-1-ol (700 mg, 71% yield) which was carried to the next step without further purification. MS: MS *m/z* 219.1 (M^++1).

Step 2:

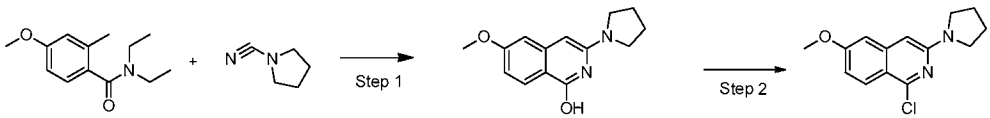
A solution of 3-(dimethylamino)-6-methoxyisoquinolin-1-ol (700 mg, 3.21 mmol) in $POCl_3$ (2 ml, 21.46 mmol) was refluxed for 4 h. The reaction mixture was concentrated. The residue was dissolved in DCM and the pH was adjusted to 7 with 4N NaOH. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using 50% DCM in hexanes as eluent. The product fractions were collected and the solvent was removed under vacuum to give 1-chloro-6-methoxy-

N,N-dimethylisoquinolin-3-amine (400 mg, 53% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 7.96 (d, *J*=9.3 Hz, 1H), 6.87 (dd, *J*=9.2, 2.4 Hz, 1H), 6.80 (d, *J*=2.3 Hz, 1H), 6.43 (s, 1H), 3.91 (s, 3H), 3.14 (s, 6H); MS *m/z* 237.0 (M^++1).

Preparation of 1-chloro-6-methoxy-3-(pyrrolidin-1-yl)isoquinoline



Scheme



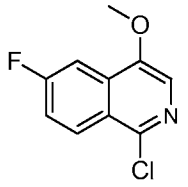
Step 1:

To a solution of N,N-diethyl-4-methoxy-2-methylbenzamide (.270 g, 1.220 mmol) in THF (10 mL) was added tert-butyllithium (1.077 mL, 1.830 mmol) dropwise at -78°C. After stirring for 0.5 h, pyrrolidine-1-carbonitrile (0.135 mL, 1.342 mmol) was added, then the solution was warmed to rt, and stirred for 16 h. The reaction mixture was quenched with MeOH, neutralized with 1.5 mL of 4.0M HCl in dioxane. Extracted product with 20 mL of DCM. The solution was evaporated on rotovap and then placed under high vacuum for 1 h to give 6-methoxy-3-(pyrrolidin-1-yl)isoquinolin-1-ol (298 mg, 100% yield) which was used in the next step without further purification. MS *m/z* 245.1 (M^++1).

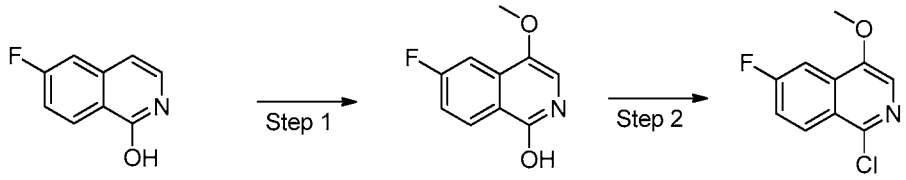
Step 2:

A solution of 6-methoxy-3-(pyrrolidin-1-yl)isoquinolin-1-ol (300 mg, 1.228 mmol) in $POCl_3$ (8 mL) was refluxed for 4 h. After concentration, the residue was taken into a mixture of 100 mL of DCM and 50 mL of water, cooled to 0°C, neutralized with 3 N NaOH, dried over MgSO4, concentrated and purified via silica gel chromatography (5-20% EtOAc:Hex) to give 1-chloro-6-methoxy-3-(pyrrolidin-1-yl)isoquinoline (156 mg, 48.3 % yield) as a yellow solid. ^{1}H NMR (500MHz, CHLOROFORM-d) δ ppm 7.95 (d, *J*=9.5 Hz, 1H), 6.85 (d, *J*=9.2 Hz, 1H), 6.80 (s, 1H), 6.43 (br. s., 1H), 3.89 (s, 3H), 3.56 - 3.49 (m, 4H), 2.08 - 2.03 (m, 4H); MS *m/z* 263.1 (M^++1).

Preparation of 1-chloro-6-fluoro-4-methoxyisoquinoline



Scheme



Step 1:

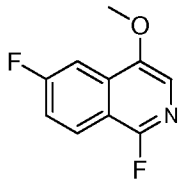
6-fluoroisoquinolin-1-ol (1 g, 6.13 mmol), iodobenzene diacetate (2.172 g, 6.74 mmol) and MeOH (15 ml) were added to a sealed tube. To the mixture was added methanesulfonic acid (0.477 ml, 7.36 mmol). The threaded stopper was affixed to the vessel and the mixture was heated first to 70 °C for 4 h and then to 130 ° C for 3 h. The mixture was concentrated in vacuo to remove half of methanol, then 5 mL of water was added and the solid was collected by filtration and washed thoroughly with 1:1 methanol/water then dried *in vacuo* to give 6-fluoro-4-methoxyisoquinolin-1-ol (800 mg, 68 % yield). ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 8.27 (dd, *J*=9.0, 5.8 Hz, 1H), 7.49 (dd, *J*=10.0, 2.5 Hz, 1H), 7.46 - 7.42 (m, 1H), 6.83 (d, *J*=6.3 Hz, 1H), 3.81 (s, 3H); MS *m/z* 194.1 (M^++1).

Step 2:

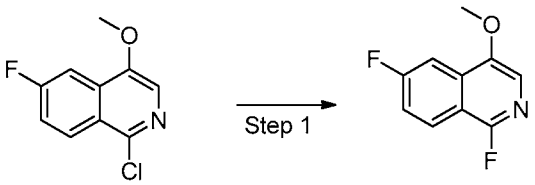
A solution of 6-fluoro-4-methoxyisoquinolin-1-ol (2.9 g, 15.01 mmol) in $POCl_3$ (10 ml, 107 mmol) was refluxed for 4 h. The reaction mixture was concentrated. The residue was dissolved in DCM and the pH was adjusted to 7 with 4N NaOH. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using 50% DCM in Hexanes as eluent. The product fractions were collected and the solvent removed under vacuum to give 1-chloro-6-fluoro-4-methoxyisoquinoline (2.2 g, 67% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.29 (dd, *J*=9.2, 5.4

Hz, 1H), 7.84 - 7.79 (m, 2H), 7.45 (ddd, *J*=9.3, 8.2, 2.6 Hz, 1H), 4.06 (s, 3H); MS *m/z* 212.0 (M^++1).

Preparation of 1,6-difluoro-4-methoxyisoquinoline



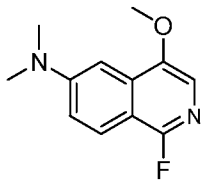
Scheme



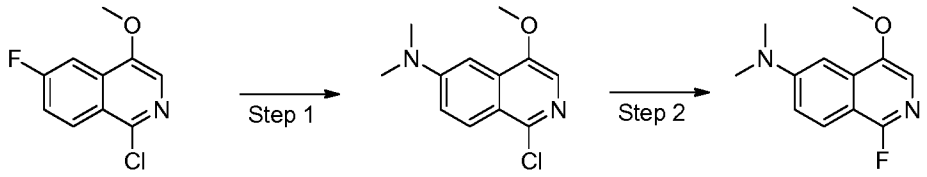
Step 1:

To a solution of 1-chloro-6-fluoro-4-methoxyisoquinoline (115 mg, 0.543 mmol) in DMSO (5 mL), was added CsF (165 mg, 1.087 mmol) and the reaction was heated to 140 °C for 2 h. The reaction was diluted with EtOAc and washed with water, and brine. The organic phase was collected, dried over sodium sulfate, and concentrated under vacuum to give the crude product which was purified by silica gel chromatography using 20-40% DCM in hexanes. The product fractions were collected and the solvent was removed under vacuum to give 1,6-difluoro-4-methoxyisoquinoline (71 mg, 67% yield). MS *m/z* 196.1 (M^++1).

Preparation of 1-fluoro-4-methoxy-N,N-dimethylisoquinolin-6-amine



Scheme



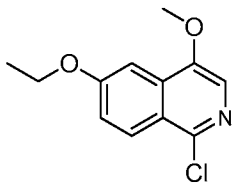
Step 1:

To 1-chloro-6-fluoro-4-methoxyisoquinoline (200 mg, 0.945 mmol) was added dimethylamine 2 M in THF (2 ml, 4.00 mmol) and the solution was heated to 100°C in a sealed tube for 16 h. The reaction was cooled and the volatiles were removed under vacuum. The crude residue was purified by silica gel chromatography using DCM as eluent. The product factions were collected and the solvent removed under vacuum to give 1-chloro-4-methoxy-N,N-dimethylisoquinolin-6-amine (150 mg, 70% yield). MS *m/z* 237.1 (M^++1).

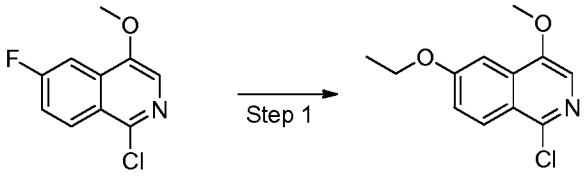
Step 2:

To a solution of 1-chloro-4-methoxy-N,N-dimethylisoquinolin-6-amine (250 mg, 1.056 mmol) in DMSO (5 mL) was added tetramethylammonium fluoride (295 mg, 3.17 mmol) and the solution was heated to 110 °C for 1 h. The reaction was diluted with Ethylacteate and washed with water, and brine. The organic phase was collected, dried over sodium sulfate, and concentrated under vacuum to give the crude product which was purified by silica gel chromatography using 80% DCM/hexanes. The product fractions were collected and the solvent removed under vacuum to give 1-fluoro-4-methoxy-N,N-dimethylisoquinolin-6-amine (130 mg, 56% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.00 (d, *J*=9.3 Hz, 1H), 7.37 (d, *J*=1.3 Hz, 1H), 7.28 - 7.24 (m, 1H), 7.17 (s, 1H), 4.04 (s, 3H), 3.20 (s, 6H); MS *m/z* 221.0 (M^++1).

Preparation of 1-chloro-6-ethoxy-4-methoxyisoquinoline



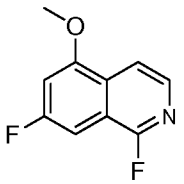
Scheme



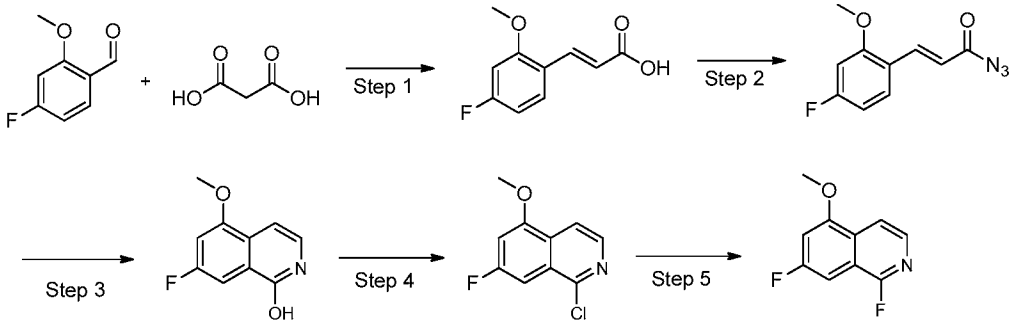
Step 1:

1-chloro-6-fluoro-4-methoxyisoquinoline (533 mg, 2.52 mmol) was dissolved in DMSO (5 mL) then NaOEt (171 mg, 2.52 mmol) was added to the solution. The reaction was stirred for 16 h. The reaction was diluted with EtOAc and washed with 1N HCl, then brine. The organic layer was collected, dried over sodium sulfate and concentrated under vacuum. The crude material was purified by silica gel chromatography using DCM as eluent. The product fractions were collected and solvent was removed under vacuum to give 1-chloro-6-ethoxy-4-methoxyisoquinoline (320 mg, 54% yield). MS *m/z* 238.0 (M^++1).

Preparation of 1,7-difluoro-5-methoxyisoquinoline



Scheme



Step 1:

A solution of 4-fluoro-2-methoxybenzaldehyde (1.0 g, 6.49 mmol) and malonic acid (1.350 g, 12.98 mmol) in pyridine (10 mL) was refluxed for 16 h. After concentration the residue was taken into water. The solid was filtered, washed with

water, then dried to give (E)-3-(4-fluoro-2-methoxyphenyl)acrylic acid (1.22 g, 96% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 8.03 (d, *J*=16.1 Hz, 1H), 7.53 (dd, *J*=8.5, 6.8 Hz, 1H), 6.75 - 6.65 (m, 2H), 6.52 (d, *J*=16.1 Hz, 1H), 3.92 (s, 3H).

Step 2:

(E)-3-(4-fluoro-2-methoxyphenyl)acrylic acid (1.22 g, 6.22 mmol), diphenylphosphinyl azide (1.273 mL, 5.91 mmol), and Et3N (1.734 mL, 12.44 mmol) were dissolved in benzene and stirred for 16 h. The solution was concentrated under vacuum and the residue was purified by silica gel chromatography using 20% EtOAc/Hexanes to give (E)-3-(4-fluoro-2-methoxyphenyl)acryloyl azide (1.0 g, 73% yield).

Step 3:

A mixture of (E)-3-(4-fluoro-2-methoxyphenyl)acryloyl azide (1g, 4.52 mmol) in $PhCH_2Ph$ (5 mL) was slowly heated to 80 °C for 1 h and then to reflux for 3 h. After cooling to RT, the solid was collected and washed with benzene to give 7-fluoro-5-methoxyisoquinolin-1-ol (383 mg, 46% yield). MS *m/z* 194.2 (M^++1).

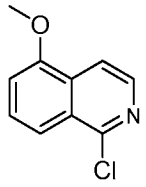
Step 4:

A solution of 7-fluoro-5-methoxyisoquinolin-1-ol (383 mg, 1.983 mmol) in $POCl_3$ (2772 µl, 29.7 mmol) was refluxed (90 °C) for 4 h. The reaction mixture was concentrated. The residue was dissolved in DCM and the pH was adjusted to 7 with 4N NaOH. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum to give 1-chloro-7-fluoro-5-methoxyisoquinoline (399 mg, 95% yield).

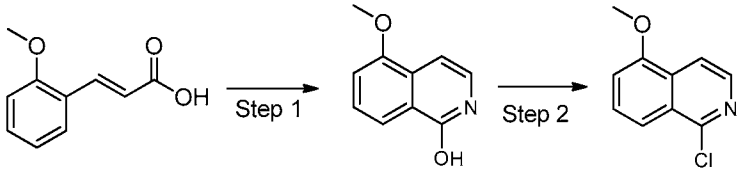
Step 5:

To a solution of 1-chloro-7-fluoro-5-methoxyisoquinoline (350 mg, 1.654 mmol) in DMSO (3 mL), was added CsF (502 mg, 3.31 mmol) and the mixture was heated to 140 °C for 4 h. The reaction was diluted with EtOAc and washed with water, and brine. The organic phase was collected, dried over sodium sulfate, and concentrated under vacuum to give 1,7-difluoro-5-methoxyisoquinoline (340 mg, 105% yield) which was not purified further. MS *m/z* 196.1 (M^++1).

Preparation of 1-chloro-5-methoxyisoquinoline



Scheme



1-chloro-5-methoxyisoquinoline was prepared by a similar method for the preparation of 1,7-difluoro-5-methoxyisoquinoline with the following modifications:

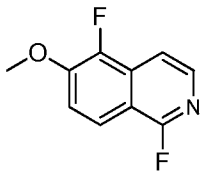
Step 1:

Modification: 10 g of (E)-3-(2-methoxyphenyl)acrylic acid was used instead of (E)-3-(4-fluoro-2-methoxyphenyl)acrylic acid which gave 5-methoxyisoquinolin-1-ol (5.3 g, 53% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 10.92 (s, 1 H), 7.43 (t, *J*=8.1 Hz, 1 H), 7.14 (d, *J*=7.3 Hz, 1 H), 7.08 (d, *J*=8.1 Hz, 1 H), 6.94 (d, *J*=7.3 Hz, 1 H), 3.95 (s, 3 H); MS *m/z* 176.1 (M^++1).

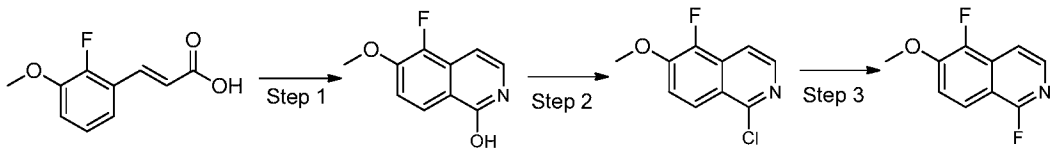
Step 2:

Modifications: 5.3 g 5-methoxyisoquinolin-1-ol used instead of 7-fluoro-5-methoxyisoquinolin-1-ol, 5.38 g 1-chloro-5-methoxyisoquinoline obtained (92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25 (d, *J*=5.9 Hz, 1 H) 7.97 (d, *J*=5.9 Hz, 1 H), 7.88 (d, *J*=8.6 Hz, 1 H), 7.57 (t, *J*=8.1 Hz, 1 H), 7.04 (d, *J*=7.8 Hz, 1 H), 4.01 (s, 3 H); MS *m/z* 194.1 (M^++1).

Preparation of 1,5-difluoro-6-methoxyisoquinoline



Scheme



1,5-difluoro-6-methoxyisoquinolinewas prepared by a similar method for the preparation of 1,7-difluoro-5-methoxyisoquinoline with the following modifications:

Step 1:

Modifications: 3.92 g (E)-3-(2-fluoro-3-methoxyphenyl)acrylic acid was used instead of (E)-3-(4-fluoro-2-methoxyphenyl)acrylic acid which gave 5-fluoro-6-methoxyisoquinolin-1-ol (2.4 g , 61% yield). ^{1}H NMR(400 MHz, CD_3OD) δ ppm 8.09 (d, *J*=8.80 Hz, 1 H), 7.35 (t, *J*=8.44 Hz, 1 H), 7.16 (d, *J*=7.34 Hz, 1 H), 6.72 (m, 1 H), 4.00 (s, 3 H).

Step 2:

Modifications: 1.93 g 5-fluoro-6-methoxyisoquinolin-1-ol was used instead of 7-fluoro-5-methoxyisoquinolin-1-ol, 1.7 g 1-chloro-5-fluoro-6-methoxyisoquinoline obtained (80% yield). ^{1}H NMR ($CDCl_3$) δ ppm 8.22 (d, *J*=5.87 Hz, 1 H), 8.12 (d, *J*=9.29 Hz, 1 H), 7.75 (d, *J*=5.87 Hz, 1 H), 7.44 (dd, *J*=9.29, 7.83 Hz, 1 H), 4.08 (s, 3 H); MS *m/z* 212.1 (M^++1).

Step 3:

To a solution of 1-chloro-5-fluoro-6-methoxyisoquinoline (0.5 g, 2.363 mmol) in DMSO (5 mL), was added CsF (0.718 g, 4.73 mmol). The mixture was heated to 140 °C for 2 h. The reaction was diluted with ethylacteate and washed with water, and brine. The organic phase was collected, dried over sodium sulfate, and concentrated under vacuum to give the crude product which was purified by silica gel chromatography using a gradient of 30-50% DCM in hexanes. The product fractions were collected and the solvent was removed under vacuum to give 1,5-difluoro-6-methoxyisoquinoline (340 mg, 74% yeild). MS *m/z* 196.2 (M^++1).

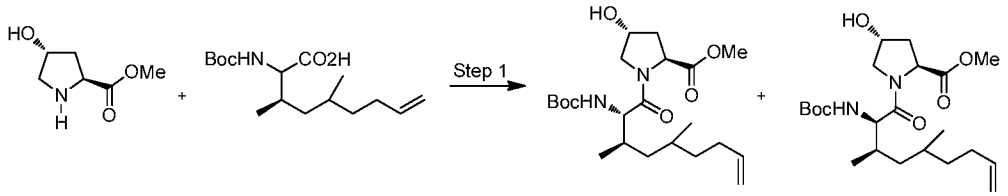
Preparation of tripeptide Intermediates:

The tripeptide intermediates described in this section can be used to prepare compounds of Formula I by the methods described herein.

Tripeptide elements:

Preparation of (2S,4R)-methyl 1-((2S,3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylate

Scheme

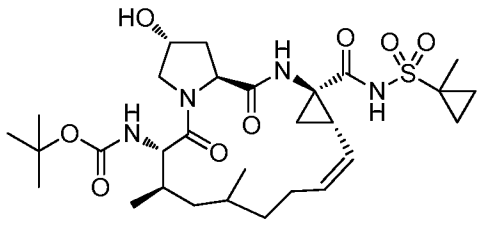


Step 1:

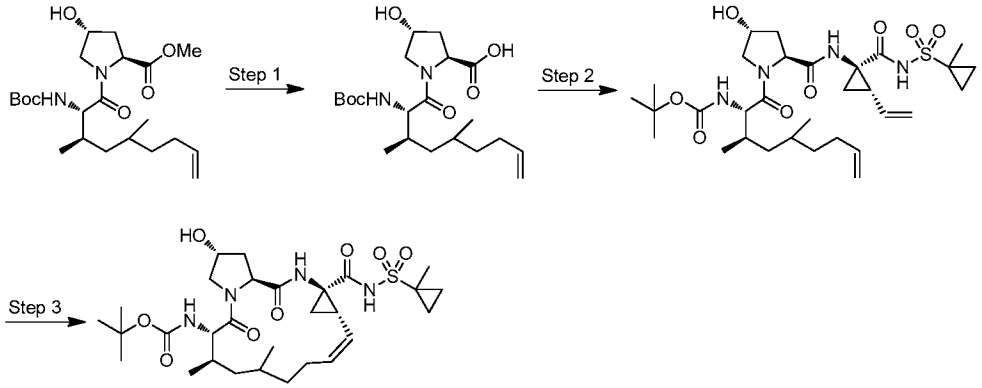
O-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HATU, 31.7 g, 83 mmol) was added to a solution of (2S,4R)-methyl 4-hydroxypyrrolidine-2-carboxylate HCl (16.68 g, 92 mmol), (3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoic acid (25 g, 83 mmol) and NEt_3 (34.9 mL, 250 mmol) in DCM (250 mL) and stirred at RT for 16 h. The reaction was washed with 1N HCl (3X) and then brine. The organics were dried with magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified via silica gel chromatography using 20-60% Acetone in hexanes to give the desired product (2S,4R)-methyl 1-((2S,3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylate (10.8 g, 30 % yield), MS: MS *m/z* 427.2 (M^++1) and the undesired product (2S,4R)-methyl 1-((2R,3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylate (12 g, 34 % yield), MS: MS *m/z* 427.2 (M^++1).

General method for the preparation of tripeptide

Preparation of tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-2-hydroxy-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate



Scheme



Step 1:

(2S,4R)-methyl 1-((2S,3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylate (10.8 g, 25.3 mmol) was dissolved in THF (50 mL), MeOH (50 mL) and to this solution was added LiOH (2.425 g, 101 mmol) in Water (50.0 mL). The reaction mixture was stirred at rt for 16 h. The solvent was removed under vacuum and the resulting aqueous residue was diluted with water, and EtOAc. The mixture was neutralised with 1 N HCl and adjusted the pH ~ 2.5 and the mixture was extracted with EtOAc. The organic layer was collected, washed with brine, dried over Na_2SO_4, and concentrated to give (2S,4R)-1-((2S,3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylic acid (12 g, 29.1 mmol, 115 % yield) as yellow viscous oil. MS: MS *m/z* 413.2 (M^++1).

Step 2:

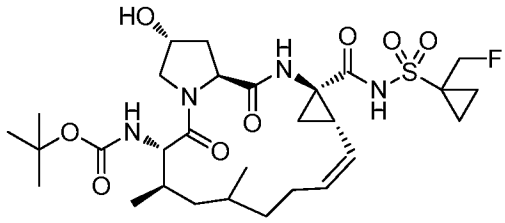
HATU (7.60 g, 20.00 mmol) was added to a solution of (2S,4R)-1-((2S,3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylic acid (7.86 g, 19.05 mmol), (1R,2S)-1-amino-N-((1-methylcyclopropyl)sulfonyl)-2-vinylcyclopropanecarboxamide HCl (5.62 g, 20 mmol), and Hunig'sBase (13.31 mL, 76 mmol) in DCM (110 mL). The reaction mixture was stirred at rt for 16 h. The reaction was washed with 1N HCl (3X), and then brine. The organic layer was collected, dried over sodium sulfate, and concentrated under vacuum. The crude material was purified by silica gel chromatography using a gradient of 20-60% Acetone in hexanes. The product fractions were collected and the solvent removed under vacuum to give tert-butyl

((2S,3R)-1-((2S,4R)-4-hydroxy-2-(((1R,2S)-1-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)pyrrolidin-1-yl)-3,5-dimethyl-1-oxonon-8-en-2-yl)carbamate (9 g, 74.0 % yield) as a light orange foam. MS: MS *m/z* 639.3 (M^++1).

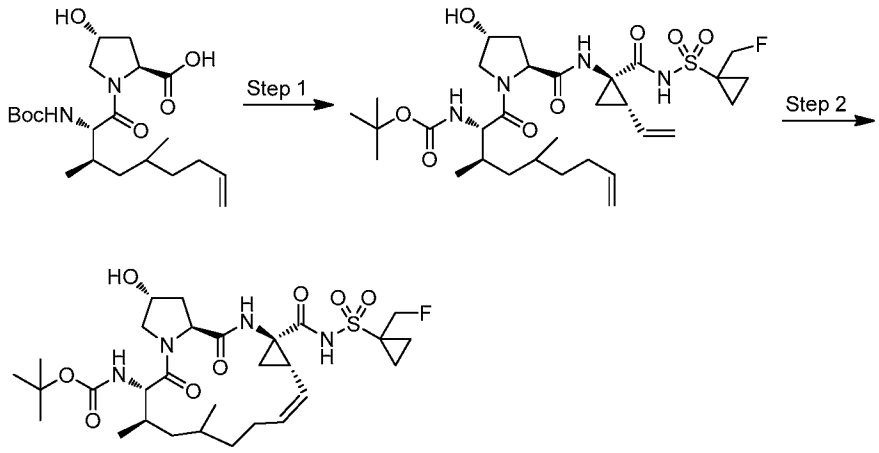
Step 3:

A solution of tert-butyl ((2S,3R)-1-((2S,4R)-4-hydroxy-2-(((1R,2S)-1-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)pyrrolidin-1-yl)-3,5-dimethyl-1-oxonon-8-en-2-yl)carbamate (8.4 g, 13.15 mmol) in DCE (1500 ml) was sparged with nitrogen for 30 min. and then (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(o-isopropoxyphenylmethylene)ruthenium)Hoveyda-Grubbs Catalyst 2nd Generation, 0.413 g, 0.657 mmol) was added. The reaction solution was heated to 80°C for 2 h. The reaction was concentrated and purified by silica gel chromatography using a gradient of 20-60% Acetone in hexanes to give tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-2-hydroxy-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate (5.6 g, 70% yield) as a brown solid. MS: MS *m/z* 611.3 (M^++1).

Preparation of tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-hydroxy-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate



Scheme



Step 1:

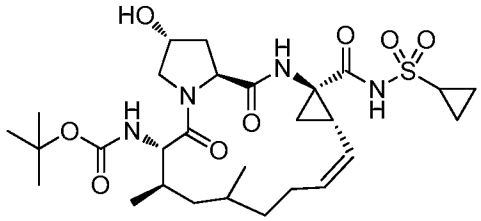
HATU (11.61 g, 30.5 mmol) was added to a solution of (2S,4R)-1-((2S,3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylic acid (10.50 g, 25.5 mmol), (1R,2S)-1-amino-N-((1-(fluoromethyl)cyclopropyl)sulfonyl)-2-vinylcyclopropanecarboxamide HCl (8.37 g, 28 mmol), and triethylamine (14.19 mL, 102 mmol) in DCM (220 mL) and was stirred at RT for overnight. The reaction was washed with 1N HCl (3X) and then brine and evaporated on rotovap. The crude material was purified by silica gel chromatography using 20-40% Acetone in hexanes. The product fractions were collected and the solvent removed under vacuum to give the desired product tert-butyl ((2S,3R)-1-((2S,4R)-2-(((1R,2S)-1-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3,5-dimethyl-1-oxonon-8-en-2-yl)carbamate (15 g, 90% yield). MS: MS *m/z* 657.3 (M^++1).

Step 2:

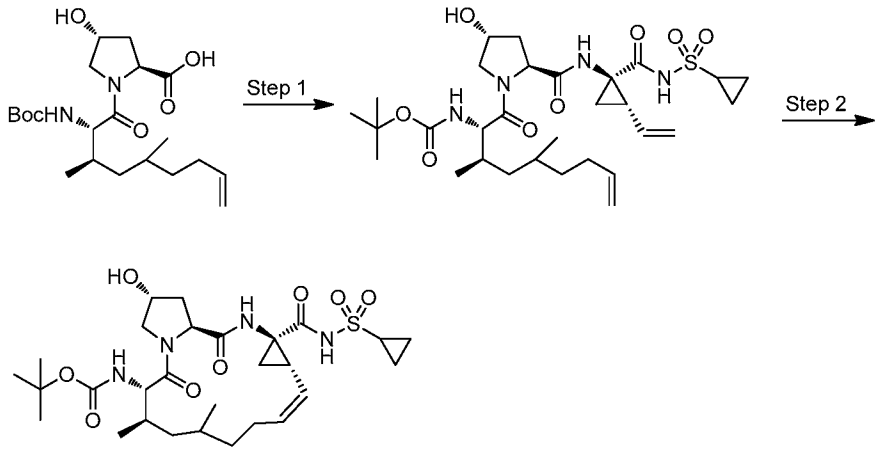
A solution of tert-butyl ((2S,3R)-1-((2S,4R)-2-(((1R,2S)-1-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3,5-dimethyl-1-oxonon-8-en-2-yl)carbamate (7.5 g, 22.84 mmol) in DCE (2855 ml) was sparged with nitrogen for 30 min. and then Hoveyda-Grubbs Catalyst 2nd Generation (0.718 g, 1.142 mmol) was added and the reaction heated to 80°C for 2 hrs. The reaction was concentrated and purified by flash chromatography on silica gel(20-60% Acetone in hexanes) to give tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-(((1-

(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-hydroxy-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate (4 g, 6.36 mmol, 27.9 % yield). MS: MS *m/z* 629.3 (M^++1).

Preparation of tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-hydroxy-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate



Scheme



Step 1:

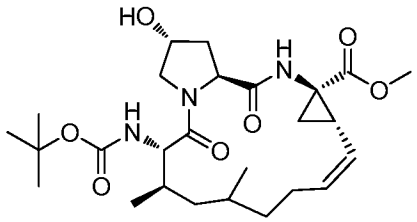
HATU (11.54 g, 30.4 mmol) was added to a solution of (2S,4R)-1-((2S,3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylic acid (10.44 g, 25.3 mmol), (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide, p-toluenesulfonate salt (11.17 g, 27.8 mmol), and Hunig'sBase (17.67 ml, 101 mmol) in DCM (200 ml) and was stirred at RT for overnight. The reaction was washed with 1N HCl (3X) and then brine and evaporated on rotovap, and purified to get the final product tert-butyl ((2S,3R)-1-((2S,4R)-2-(((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-

vinylcyclopropyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3,5-dimethyl-1-oxonon-8-en-2-yl)carbamate (14.8 g, 23.69 mmol, 94 % yield) as a light orange foam.

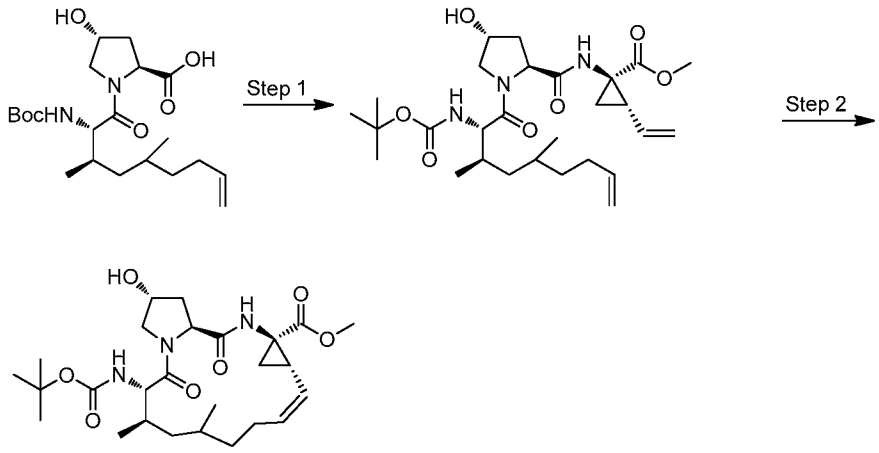
Step 2:

A solution of tert-butyl ((2S,3R)-1-((2S,4R)-2-(((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3,5-dimethyl-1-oxonon-8-en-2-yl)carbamate (9.5 g, 15.21 mmol) in DCE (2500 ml) was sparged with nitrogen for 30 min. and then Hoveyda-Grubbs Catalyst 2nd Generation (0.574 g, 0.912 mmol) was added and the reaction heated to 80°C for 2 hrs then cooled down to 45°C and stirred for 2 days. The reaction was concentrated and purified by flash chromatography on silica gel(20-60% Acetone in hexanes) to give the product tert-Butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-hydroxy-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate (7 g). MS: MS *m/z* 597.35 (M^++1).

Preparation of (2R,6S,7R,13aS,14aR,16aS,Z)-methyl 6-((tert-butoxycarbonyl)amino)-2-hydroxy-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate



Scheme



Step 1:

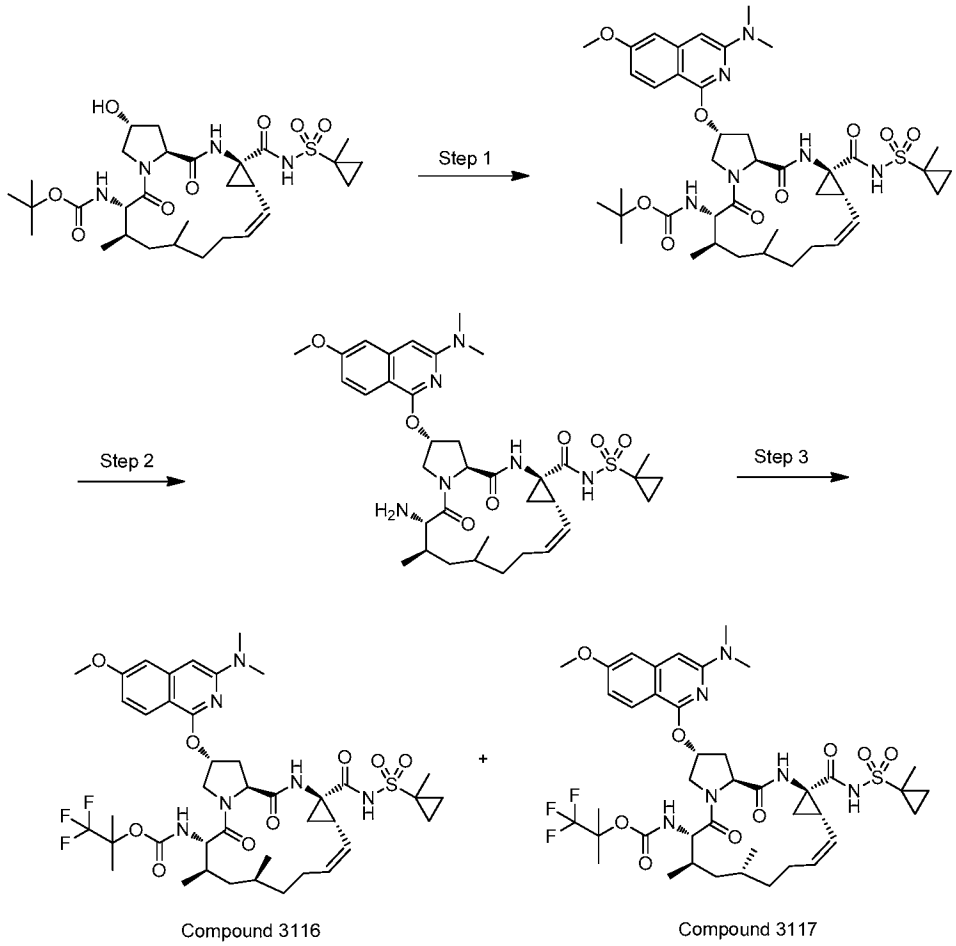
HATU (2.510 g, 6.60 mmol) was added to a solution of (2S,4R)-1-((2S,3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylic acid (2.269 g, 5.5 mmol), (1R,2S)-methyl 1-amino-2-vinylcyclopropanecarboxylate HCl (1.172 g, 6.60 mmol), and Hunig'sBase (3.84 ml, 22.00 mmol) in DCM (20 ml) and was stirred at RT for overnight. The reaction was washed with 1N HCl (3X) and then brine and evaporated on rotovap, then purified via silica gel chromatography to get the product (1R,2S)-methyl 1-((2S,4R)-1-((2S,3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate (2.68 g, 5.00 mmol, 91 % yield) as a light orange foam.MS: MS *m/z* 558.16 (M^++23).

Step 2:

A solution of (1R,2S)-methyl 1-((2S,4R)-1-((2S,3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate (2.68 g, 5 mmol) in DCE (600 mL) was sparged with nitrogen for 30 min. and then Hoveyda-Grubbs Catalyst 2nd Generation (0.189 g, 0.300 mmol) was added and the reaction heated to 80°C for 2 hrs. The reaction was concentrated and purified by flash chromatography on silica gel(20-60% Acetone in hexanes) to give 2.1 g of the product (2R,6S,7R,13aS,14aR,16aS,Z)-methyl 6-((tert-butoxycarbonyl)amino)-2-hydroxy-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate. MS: MS *m/z* 530.18 (M^++23).

Preparation of Compound 3116 and Compound 3117

Scheme



Step 1:

To a mixture of tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-2-hydroxy-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate (150 mg, 0.246 mmol),1-chloro-6-methoxy-N,N-dimethylisoquinolin-3-amine (69.8 mg, 0.295 mmol), and potassium tert-butoxide (138 mg, 1.228 mmol) was added DMSO (5 mL) and then the mixture was sonicated for 15 min. The resulting solution was stirred for 4h at room temperature. The reaction was quenched with water, acidified with 6 N HCl to pH = 4, and extracted with EtOAc. The organic layer was collected, washed with brine, dried over MgSO4, filtered, and concentrated to give the crude tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate that was used in the next step as is. MS: MS *m/z* 811.6 (M^++1).

Step 2:

tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate (50 mg, 0.062 mmol) was dissolved in DCM (4 mL) and trifluoroacetic acid (TFA, 1 ml, 12.98 mmol) was added. The reaction was stirred for 1 h at room temperature. The volatiles were removed under vacuum to give (2R,6S,7R,13aS,14aR,16aS,Z)-6-amino-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide TFA (51 mg) which was used in the next step as is. MS: MS *m/z* 711.1 (M^++1).

Step 3:

To a solution of (2R,6S,7R,13aS,14aR,16aS,Z)-6-amino-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide TFA (50 mg, 0.070 mmol) and pyridin-2-yl (1,1,1-trifluoro-2-methylpropan-2-yl) carbonate (21.03 mg, 0.084 mmol) in CH_2Cl_2 (1 mL) was added N-ethyl-N-isopropylpropan-2-amine (Hunig's Base, 0.061 mL, 0.352 mmol). The reaction was stirred for 16 h. After concentration the crude material was purified via preparative HPLC as follows: Column: Waters XBridge C18, 19 x 200 mm, 5-μm particles; Guard Column: Waters XBridge C18, 19 x 10 mm, 5-μm particles; Mobile Phase A: water; Mobile Phase B: acetonitrile; Buffer: 20-mM ammonium acetate; Gradient: 20-95% B over 20.5 minutes, then a 7.0 minute hold at 95% B; Flow: 25 mL/min. Compound 3116 eluted first under the described conditions, followed by Compound 3117. Fractions containing pure Compound 3116 were pooled and concentrated via centrifugal evaporation to give

to 5.0 mg of Compound 3116 as a solid; fractions containing pure Compound 3117 were pooled and concentrated via centrifugal evaporation to give 8.6 mg of Compound 3117 as a solid.

Compound 3116: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 865.5 (M^++1).

Compound 3117: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) 11.05 (br. s., 1H), 9.11 (br. s., 1H), 7.86 (d, *J*=7.9 Hz, 1H), 7.76 (d, *J*=9.2 Hz, 1H), 6.95 (d, *J*=2.4 Hz, 1H), 6.65 (dd, *J*=9.2, 2.4 Hz, 1H), 6.23 (s, 1H), 5.77 (br. s., 1H), 5.60 - 5.46 (m, 1H), 5.03 - 4.92 (m, 1H), 4.53 - 4.40 (m, 2H), 3.95 (dd, *J*=11.4, 3.5 Hz, 1H), 3.83 (s, 3H), 3.76 (dd, *J*=10.7, 8.2 Hz, 1H), 3.07 (s, 6H), 2.73 - 2.58 (m, 2H), 2.39 - 2.25 (m, 2H), 1.97 - 1.81 (m, 2H), 1.75 - 1.08 (m, 17H), 0.99 - 0.85 (m, 8H), 0.76 (t, *J*=11.7 Hz, 1H); MS: MS *m/z* 865.5 (M^++1).

Crystal Structure Data of Compound 3117

Crystallization Conditions for Compound 3117

10 mg of Compound 3117 was dissolved in 1.5ml methanol. The resultant solution was slow evaporated at 2-5°C to afford the solid crystalline form.

Cell dimensions:

a = 14.7856(2)Å

b = 24.3272(2)Å

c = 25.8319(2)Å

α = 90.0°

β = 90.0°

γ = 90.0°

Space group: $P2_12_12_1$

Molecules of Compound/asymmetric unit: 2

Volume = 9292(2) $Å^3$

Density (calculated) = 1.294 g/cm^3

Measurement of said crystalline form is at a temperature of about -123°C.

Single Crystal X-Ray Measurements:

A Bruker SMART APEX II diffractometer equipped with graphite-monochromated Mo Kα radiation, (λ = 0.71073 Å) was used to collect diffraction data at -123°C. A full data set was collected using the ω scan mode over the 2θ range with a crystal-to-detector distance of 4.0 cm. An empirical absorption correction utilized the SADABS routine associated with the diffractometer (Bruker AXS. 1998, SMART and SAINTPLUS. Area Detector Control and Integration Software, Bruker AXS, Madison, Wisconsin, USA). The final unit cell parameters were determined using the entire data set.

All structures were solved by direct methods and refined by the full-matrix least-squares techniques, using the SHELXTL software package (Sheldrick, G.M., 2008, SHELXTL. Structure Determination Programs. Version 6.10, Bruker AXS, Madison, Wisconsin, USA.). The function minimized in the refinements was $\Sigma_w(|F_o| - |F_c|)^2$. R is defined as $\Sigma ||F_o| - |F_c||/\Sigma |F_o|$, while $R_w = [\Sigma_w(|F_o| - |F_c|)^2/\Sigma_w |F_o|^2]^{1/2}$, where w is an appropriate weighting function based on errors in the observed intensities.

Difference FOURIER® maps were examined at all stages of refinement. All non-hydrogen atoms were refined with anisotropic thermal displacement parameters. The hydrogen atoms associated with hydrogen bonding were located in the final difference FOURIER® maps while the positions of the other hydrogen atoms were calculated from an idealized geometry with standard bond lengths and angles. They were assigned isotropic temperature factors and included in structure factor calculations with fixed parameters.

Table 1. Fractional Atomic Coordinates for Compound 3117 at T= -123 °C

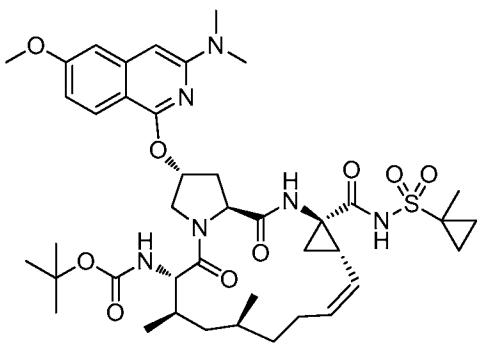
Atom	x	y	z	Atom	x	y	z
S(1A)	0.0898(2)	0.2239(1)	0.0621(1)	S(1B)	0.3016(2)	0.1467(1)	0.4300(1)
F(1A)	0.2852(4)	0.6576(2)	0.3427(2)	F(1B)	0.3698(4)	0.5653(3)	0.1181(2)
F(2A)	0.2178(4)	0.7290(2)	0.3719(2)	F(2B)	0.3228(4)	0.6371(2)	0.1560(2)
F(3A)	0.2678(4)	0.7276(2)	0.2935(2)	F(3B)	0.4524(4)	0.6380(3)	0.1207(2)

O(1A)	-0.0071(5)	0.2396(3)	0.0678(2)	O(1B)	0.3293(4)	0.0911(2)	0.4185(2)
O(2A)	0.1222(6)	0.1744(2)	0.0831(2)	O(2B)	0.3596(4)	0.1813(2)	0.4606(2)
O(3A)	0.2893(5)	0.2421(2)	0.0952(2)	O(3B)	0.1978(4)	0.1244(2)	0.3297(2)
O(4A)	0.1992(4)	0.4762(2)	0.1854(2)	O(4B)	0.2902(4)	0.3672(2)	0.2663(2)
O(5A)	0.0818(4)	0.3723(2)	0.1219(2)	O(5B)	0.3271(3)	0.2855(2)	0.3539(2)
O(6A)	-0.0636(4)	0.4491(2)	0.2816(2)	O(6B)	0.6104(3)	0.3665(2)	0.2810(2)
O(7A)	0.0227(5)	0.6145(2)	0.2482(2)	O(7B)	0.4462(4)	0.5345(2)	0.2943(2)
O(8A)	0.1646(4)	0.6437(2)	0.2677(2)	O(8B)	0.3675(3)	0.5559(2)	0.2211(2)
O(9A)	-0.0259(4)	0.5403(2)	0.5073(2)	O(9B)	0.7840(5)	0.4716(2)	0.0805(2)
N(1A)	0.1456(6)	0.2754(3)	0.0901(2)	N(1B)	0.2903(4)	0.1811(2)	0.3753(2)
N(2A)	0.0519(4)	0.4568(2)	0.1952(2)	N(2B)	0.4219(4)	0.3686(2)	0.3084(2)
N(3A)	0.1988(5)	0.3474(2)	0.1729(2)	N(3B)	0.3335(4)	0.2353(2)	0.2809(2)
N(4A)	-0.1351(4)	0.3777(3)	0.3226(2)	N(4B)	0.6583(4)	0.4504(3)	0.3138(3)
N(5A)	-0.2061(5)	0.3052(3)	0.3643(2)	N(5B)	0.7005(5)	0.5342(3)	0.3476(3)
N(6A)	0.1453(4)	0.5867(2)	0.2031(2)	N(6B)	0.3221(4)	0.4865(2)	0.2694(2)
C(1A)	0.1035(11)	0.1759(5)	-0.0317(4)	C(1B)	0.1950(5)	0.1462(3)	0.4586(3)
C(2A)	0.2056(11)	0.2025(5)	-0.0184(5)	C(2B)	0.1837(6)	0.1027(3)	0.5000(3)
C(3A)	0.1146(8)	0.2297(4)	-0.0029(3)	C(3B)	0.1379(6)	0.0977(3)	0.4491(3)
C(4A)	0.814(10)	0.2806(5)	-0.0283(4)	C(4B)	0.1529(7)	0.2016(3)	0.4636(3)
C(5A)	0.2336(8)	0.2767(3)	0.1039(3)	C(5B)	0.2440(6)	0.1651(3)	0.3315(3)
C(6A)	0.2573(6)	0.3297(3)	0.1316(3)	C(6B)	0.2492(5)	0.2067(3)	0.2887(3)
C(7A)	0.3551(7)	0.3455(4)	0.1378(4)	C(7B)	0.1910(5)	0.1966(3)	0.2426(3)
C(8A)	0.2980(7)	0.3758(3)	0.0980(3)	C(8B)	0.1646(5)	0.2413(3)	0.2795(3)
C(9A)	0.3114(7)	0.3684(4)	0.0411(4)	C(9B)	0.0845(5)	0.2373(3)	0.3126(3)
C(10A)	0.2687(9)	0.3925(5)	0.0056(4)	C(10B)	0.0523(5)	0.2766(3)	0.3435(3)
C(11A)	0.1703(8)	0.4224(4)	0.0105(4)	C(11B)	0.0938(5)	0.3313(3)	0.3501(2)
C(12A)	0.1880(8)	0.4797(4)	0.0113(3)	C(12B)	0.1195(6)	0.3422(3)	0.4073(3)
C(13A)	0.1069(7)	0.5171(3)	0.0185(3)	C(13B)	0.1535(6)	0.3988(3)	0.4203(3)
C(14A)	0.0285(8)	0.5055(5)	-0.0183(4)	C(14B)	0.1656(7)	0.4014(4)	0.4796(3)
C(15A)	0.0747(6)	0.5187(3)	0.0753(3)	C(15B)	0.2438(6)	0.4135(3)	0.3931(3)
C(16A)	0.1260(6)	0.5592(3)	0.1111(3)	C(16B)	0.2344(5)	0.4492(3)	0.3445(3)
C(17A)	0.1104(6)	0.6193(3)	0.0960(3)	C(17B)	0.2084(6)	0.5076(3)	0.3576(3)
C(18A)	0.0970(5)	0.5502(3)	0.1673(3)	C(18B)	0.3218(5)	0.4491(3)	0.3134(3)
C(19A)	0.1186(6)	0.4917(3)	0.1835(3)	C(19B)	0.3429(6)	0.3914(3)	0.2939(3)
C(20A)	0.0759(5)	0.4002(3)	0.2106(2)	C(20B)	0.4405(5)	0.3109(3)	0.2929(3)
C(21A)	0.1181(6)	0.3719(3)	0.1642(3)	C(21B)	0.3621(5)	0.2766(3)	0.3109(3)
C(22A)	-0.0164(5)	0.3740(3)	0.2235(3)	C(22B)	0.5286(5)	0.2977(3)	0.3228(3)
C(23A)	-0.0799(6)	0.4231(3)	0.2324(3)	C(23B)	0.5715(6)	0.3544(3)	0.3303(3)

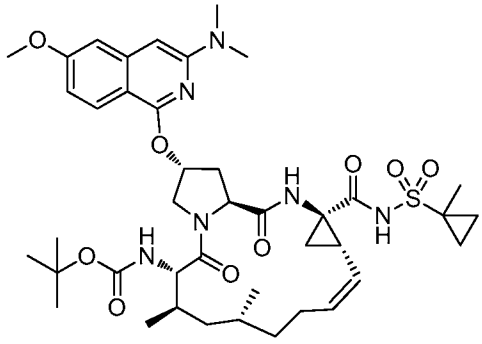
C(24A)	-0.0459(5)	0.4651(3)	0.1937(3)	C(24B)	0.4931(5)	0.3910(3)	0.3416(3)
C(25A)	-0.0946(5)	0.4256(3)	0.3254(3)	C(25B)	0.6502(5)	0.4174(3)	0.2744(3)
C(26A)	-0.1578(5)	0.3532(3)	0.3686(3)	C(26B)	0.6960(6)	0.5010(3)	0.3049(3)
C(27A)	-0.1358(5)	0.3769(3)	0.4164(3)	C(27B)	0.7248(5)	0.5162(3)	0.2575(3)
C(28A)	-0.0966(5)	0.4295(3)	0.4175(3)	C(28B)	0.7177(5)	0.4812(3)	0.2153(3)
C(29A)	-0.0785(5)	0.4563(3)	0.4652(3)	C(29B)	0.7467(6)	0.4941(3)	0.1645(3)
C(30A)	-0.0461(6)	0.5090(3)	0.4644(3)	C(30B)	0.7449(6)	0.4559(4)	0.1269(3)
C(31A)	-0.0308(5)	0.5365(3)	0.4173(3)	C(31B)	0.7103(7)	0.4039(4)	0.1349(3)
C(32A)	-0.0447(5)	0.5105(3)	0.3718(3)	C(32B)	0.6767(6)	0.3900(3)	0.1834(3)
C(33A)	-0.0779(5)	0.4561(3)	0.3710(3)	C(33B)	0.6772(5)	0.4280(3)	0.2232(3)
C(34A)	-0.0323(7)	0.5132(3)	0.5565(3)	C(34B)	0.7814(11)	0.4346(5)	0.0391(4)
C(35A)	-0.2071(6)	0.2750(3)	0.3159(3)	C(35B)	0.7480(7)	0.5860(3)	0.3432(3)
C(36A)	-0.2215(7)	0.2722(3)	0.4097(3)	C(36B)	0.6922(7)	0.5117(3)	0.3994(3)
C(37A)	0.1024(7)	0.6141(3)	0.2403(3)	C(37B)	0.3851(7)	0.5253(3)	0.2654(3)
C(38A)	0.1363(7)	0.6754(3)	0.3129(3)	C(38B)	0.4409(6)	0.5870(3)	0.1979(3)
C(39A)	0.0971(6)	0.6402(3)	0.3541(3)	C(39B)	0.5194(6)	0.5509(5)	0.1869(4)
C(40A)	0.0757(6)	0.7230(3)	0.2987(3)	C(40B)	0.4628(8)	0.6372(4)	0.2310(4)
C(41A)	0.2262(8)	0.6972(4)	0.3292(4)	C(41B)	0.3965(7)	0.6065(4)	0.1477(4)
O(1W)	0.4115(4)	0.2148(2)	0.1796(2)	O(4W)	0.4776(5)	0.1146(3)	0.1411(2)
O(2W)	-0.0760(20)	0.3406(11)	0.0561(8)	O(5W)	0.4208(12)	0.3006(6)	0.4566(5)
O(3W)	0.3819(15)	0.1445(8)	0.0508(6)	H(1B)	0.3170	0.2135	0.3739
H(1A)	0.1140	0.3052	0.0967	H(2BA)	0.2356	0.0781	0.5071
H(1AA)	0.0835	0.1433	-0.0118	H(2BB)	0.1461	0.1118	0.5305
H(1AB)	0.0820	0.1773	-0.0680	H(3B)	0.3680	0.2251	0.2548
H(2AA)	0.2422	0.1849	0.0092	H(3BA)	0.1610	0.0695	0.4247
H(2AB)	0.2406	0.2190	-0.0471	H(3BB)	0.0716	0.1032	0.4481
H(3A)	0.2163	0.3421	0.2051	H(4BA)	0.1382	0.2158	0.4292
H(4AA)	0.0152	0.2818	-0.0265	H(4BB)	0.0975	0.1988	0.4843
H(4AB)	0.1006	0.2809	-0.0646	H(4BC)	0.1953	0.2266	0.4808
H(4AC)	0.1066	0.3128	-0.0105	H(6B)	0.2803	0.4834	0.2453
H(6A)	0.2042	0.5906	0.1998	H(7BA)	0.1538	0.1627	0.2423
H(7AA)	0.4013	0.3196	0.1248	H(7BB)	0.2148	0.2077	0.2083
H(7AB)	0.3724	0.3657	0.1696	H(8B)	0.1773	0.2792	0.2666
H(8A)	0.2797	0.4138	0.1085	H(9B)	0.0524	0.2035	0.3120
H(9A)	0.3566	0.3429	0.0307	H(10)	0.2967	0.3934	-0.0275
H(10A)	-0.0011	0.2688	0.3626	H(11A)	0.1315	0.4128	-0.0194
H(11C)	0.1487	0.3338	0.3283	H(11B)	0.1393	0.4109	0.0427
H(11D)	0.0508	0.3599	0.3383	H(12A)	0.2180	0.4897	-0.0216

H(12C)	0.1667	0.3153	0.4174	H(12B)	0.2314	0.4872	0.0396
H(12D)	0.0657	0.3347	0.4290	H(13)	0.1283	0.5551	0.0102
H(13A)	0.1066	0.4262	0.4099	H(14A)	-0.065	0.4742	-0.0053
H(14D)	0.2127	0.3755	0.4903	H(14B)	0.0522	0.4969	-0.0527
H(14E)	0.1084	0.3918	0.4966	H(14C)	-0.0106	0.5379	-0.0203
H(14F)	0.1832	0.4388	0.4897	H(15A)	0.0803	0.4812	0.0899
H(15C)	0.2749	0.3790	0.3835	H(15B)	0.0097	0.5285	0.0756
H(15D)	0.2830	0.4331	0.4182	H(16)	0.1922	0.5512	0.1083
H(16A)	0.1855	0.4332	0.3224	H(17A)	0.1196	0.6237	0.0586
H(17D)	0.2012	0.5289	0.3257	H(17B)	0.0485	0.6300	0.1050
H(17E)	0.1513	0.5077	0.3769	H(17C)	0.1533	0.6428	0.1147
H(17F)	0.2559	0.5243	0.3789	H(18)	0.0304	0.5566	0.1706
H(18A)	0.3719	0.4605	0.3372	H(20)	0.1174	0.3998	0.2412
H(20A)	0.4495	0.3076	0.2546	H(22A)	-0.0381	0.3510	0.1944
H(22C)	0.5686	0.2732	0.3024	H(22B)	-0.0123	0.3509	0.2550
H(22D)	0.5152	0.2801	0.3565	H(23)	-0.1450	0.4135	0.2270
H(23A)	0.6174	0.3547	0.3587	H(24A)	-0.0704	0.4580	0.1587
H(24C)	0.4758	0.3890	0.3786	H(24B)	-0.0623	0.5029	0.2044
H(24D)	0.5068	0.4296	0.3325	H(27)	-0.1472	0.3576	0.4477
H(27A)	0.7505	0.5516	0.2528	H(29)	-0.0887	0.4379	0.4971
H(29A)	0.7678	0.5301	0.1569	H(31)	-0.0106	0.5735	0.4176
H(31A)	0.7094	0.3779	0.1075	H(32)	-0.0322	0.5290	0.3402
H(32A)	0.6532	0.3542	0.1892	H(34A)	0.0115	0.4830	0.5579
H(34D)	0.7334	0.4076	0.0450	H(34B)	-0.0935	0.4986	0.5611
H(34E)	0.7694	0.4547	0.0070	H(34C)	-0.0191	0.5396	0.5842
H(34F)	0.8398	0.4157	0.0365	H(35A)	-0.1510	0.2538	0.3125
H(35D)	0.7141	0.6107	0.3203	H(35B)	-0.2589	0.2499	0.3154
H(35E)	0.8084	0.5796	0.3287	H(35C)	-0.2119	0.3008	0.2869
H(35F)	0.7537	0.6028	0.3775	H(36A)	-0.2703	0.2460	0.4028
H(36D)	0.6553	0.4782	0.3983	H(36B)	-0.1660	0.2521	0.4184
H(36E)	0.6633	0.5388	0.4220	H(36C)	-0.2385	0.2960	0.4387
H(36F)	0.7525	0.5028	0.4128	H(39A)	0.0391	0.6252	0.3424
H(39D)	0.4979	0.5156	0.1733	H(39B)	0.1388	0.6099	0.3618
H(39E)	0.5535	0.5446	0.2189	H(39C)	0.0876	0.6621	0.3855
H(39F)	0.5587	0.5685	0.1613	H(40A)	0.0179	0.7089	0.2857
H(40D)	0.4064	0.6540	0.2433	H(40B)	0.1048	0.7452	0.2719
H(40E)	0.4994	0.6260	0.2608	H(40C)	0.0649	0.7457	0.3294
H(40F)	0.4966	0.6640	0.2103				

Preparation of Compound 3108 and Compound 3109



Compound 3108



Compound 3109

Step 1:

A diastereomeric mixture of tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate (50 mg) was purified via preparative HPLC with the following conditions: Column: Waters XBridge C18, 19 x 200 mm, 5-µm particles; Guard Column: Waters XBridge C18, 19 x 10 mm, 5-µm particles; Mobile Phase A: water with 20-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 20-mM ammonium acetate; Gradient: 60-100% B over 12 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. The diastereomers were separated and concentrated under centrifugal evaporation to give Compound 3108 (6.9 mg) and Compound 3109 (8.0 mg) respectively.

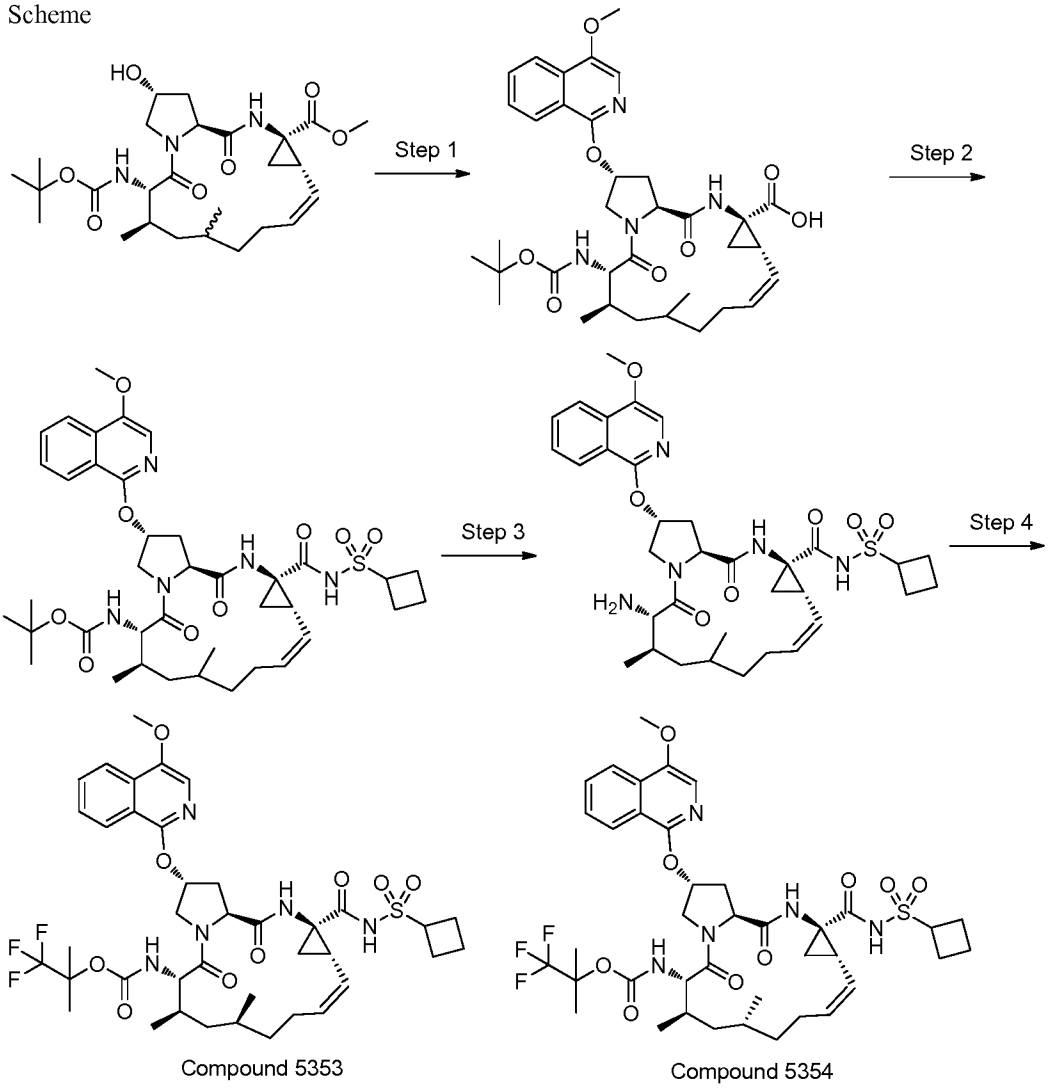
Compound 3108: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 811.7 (M^++1).

Compound 3109: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ

11.06 (br. s., 1H), 9.07 (br. s., 1H), 7.79 (d, *J*=8.9 Hz, 1H), 7.21 (d, *J*=6.1 Hz, 1H), 6.94 (d, *J*=2.4 Hz, 1H), 6.62 (dd, *J*=9.2, 2.4 Hz, 1H), 6.23 (s, 1H), 5.75 (br. s., 1H), 5.59 - 5.46 (m, 1H), 5.08 - 4.94 (m, 1H), 4.58 - 4.36 (m, 2H), 3.95 (dd, *J*=11.3, 3.7 Hz, 1H), 3.83 (s, 3H), 3.77 (dd, *J*=10.4, 8.9 Hz, 1H), 3.07 (s, 6H), 2.73 - 2.56 (m, 2H), 2.41 - 2.23 (m, 2H), 1.96 - 0.81 (m, 30H), 0.73 (br. t, *J*=12.4 Hz, 1H); MS: MS *m/z* 811.6 (M^++1).

Preparation of Compound 5353 and Compound 5354

Scheme



Step 1

To a mixture of (2R,6S,7R,13aS,14aR,16aS,Z)-methyl 6-((tert-butoxycarbonyl)amino)-2-hydroxy-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate (152 mg, 0.3 mmol),1-fluoro-4-methoxyisoquinoline (128 mg, 0.720 mmol), and t-BuOK (168 mg, 1.500 mmol) was added DMSO (5 mL) and then sonicated for 15 min. The resulting solution was stirred for 4 h. The reaction was quenched with water, acidified with 6 N HCl, extracted with EtOAc, washed with brine, dried over MgSO4. After concentration, the residue (2R,6S,7R,13aS,14aR,16aS,Z)-6-((tert-butoxycarbonyl)amino)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylic acid was obtained as a solid (150 mg) that will be used as it is. LC/MS: MS *m/z* $(M+H)^+$ 651.23.

Step 2

A mixture of (2R,6S,7R,13aS,14aR,16aS,Z)-6-((tert-butoxycarbonyl)amino)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylic acid (70 mg, 0.108 mmol), CDI (34.9 mg, 0.215 mmol) in tetrahydrofuran (3 mL) was refluxed for 2 h. It was then cooled to rt and cyclobutanesulfonamide (32.0 mg, 0.237 mmol) was added and followed by DBU (0.036 mL, 0.237 mmol). The mixture was stirred at rt for 16h. It was then concentrated and purified by silica gel chromatography, eluting with 40% acetone/hexane to isolate 70 mg of the diastereomers tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-((cyclobutylsulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate that was used as it was.

Step 3

To a solution of tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-((cyclobutylsulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate

(50 mg, 0.065 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.050 mL, 0.651 mmol). The resulting solution was stirred for 1h and concentrated to give 51 mg of a crude product (2R,6S,7R,13aS,14aR,16aS,Z)-6-amino-N-(cyclobutylsulfonyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide TFA that was used in the next step as it is. . LC/MS: MS *m/z* $(M+H)^+$ 668.32.

Step 4

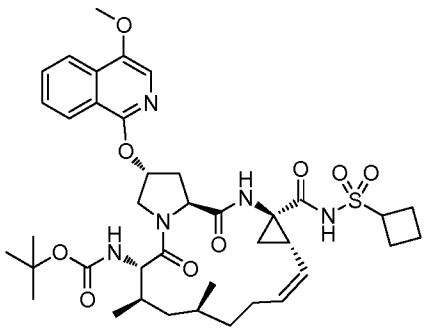
A solution of (2R,6S,7R,13aS,14aR,16aS,Z)-6-amino-N-(cyclobutylsulfonyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, TFA (46.9 mg, 0.06 mmol), pyridin-2-yl (1,1,1-trifluoro-2-methylpropan-2-yl) carbonate (17.94 mg, 0.072 mmol), and N-ethyl-N-isopropylpropan-2-amine (0.052 mL, 0.300 mmol) in CH_2Cl_2 (1 mL) was stirred for 16 h. After concentration, the residue was purified by prep HPLC to give 12.2 mg of Compound 5353 as a solid and 17.2 mg of Compound 5354 as a solid, respectively.

Compound 5353: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclobutylsulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. LC/MS: MS *m/z* $(M+H)^+$ 822.5.

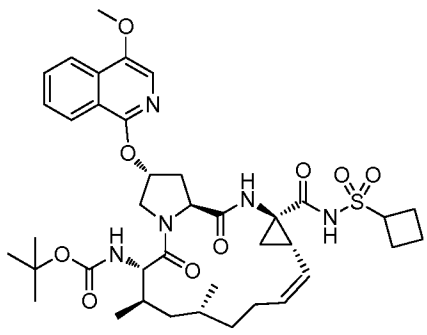
Compound 5354: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclobutylsulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.05 (s, 1H), 9.05 (br. s., 1H), 8.08 (dd, J=11.7, 8.4 Hz, 2H), 7.86 - 7.76 (m, 2H), 7.69 - 7.55 (m, 2H), 5.77 (br. s., 1H), 5.53 (d, J=6.1 Hz, 1H), 5.00 (t, J=9.9 Hz, 1H), 4.61 - 4.45 (m, 2H), 4.28 - 4.16 (m, 1H), 3.98 (s, 3H), 3.90 (dd, J=11.7, 3.8 Hz, 1H), 3.70 (dd, J=10.8, 8.1 Hz, 1H), 2.71 - 2.59 (m, 2H), 2.43 - 2.14 (m, 7H), 2.02 - 1.79

(m, 5H), 1.75 - 1.01 (m, 10H), 0.93 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.4 Hz, 3H), 0.74 (t, J=12.4 Hz, 1H); LC/MS: MS *m/z* $(M+H)^+$ 822.5.

Preparation of Compound 5351 and Compoun 5352



Compound 5351



Compound 5352

Step 1

A diastereomer mixture tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-((cyclobutylsulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate (23.6 mg) was purified by prep HLC to give 1.6 mg of Compound 5351 as a solid and 6.1 mg of the Compound 5352 as a solid, respectively.

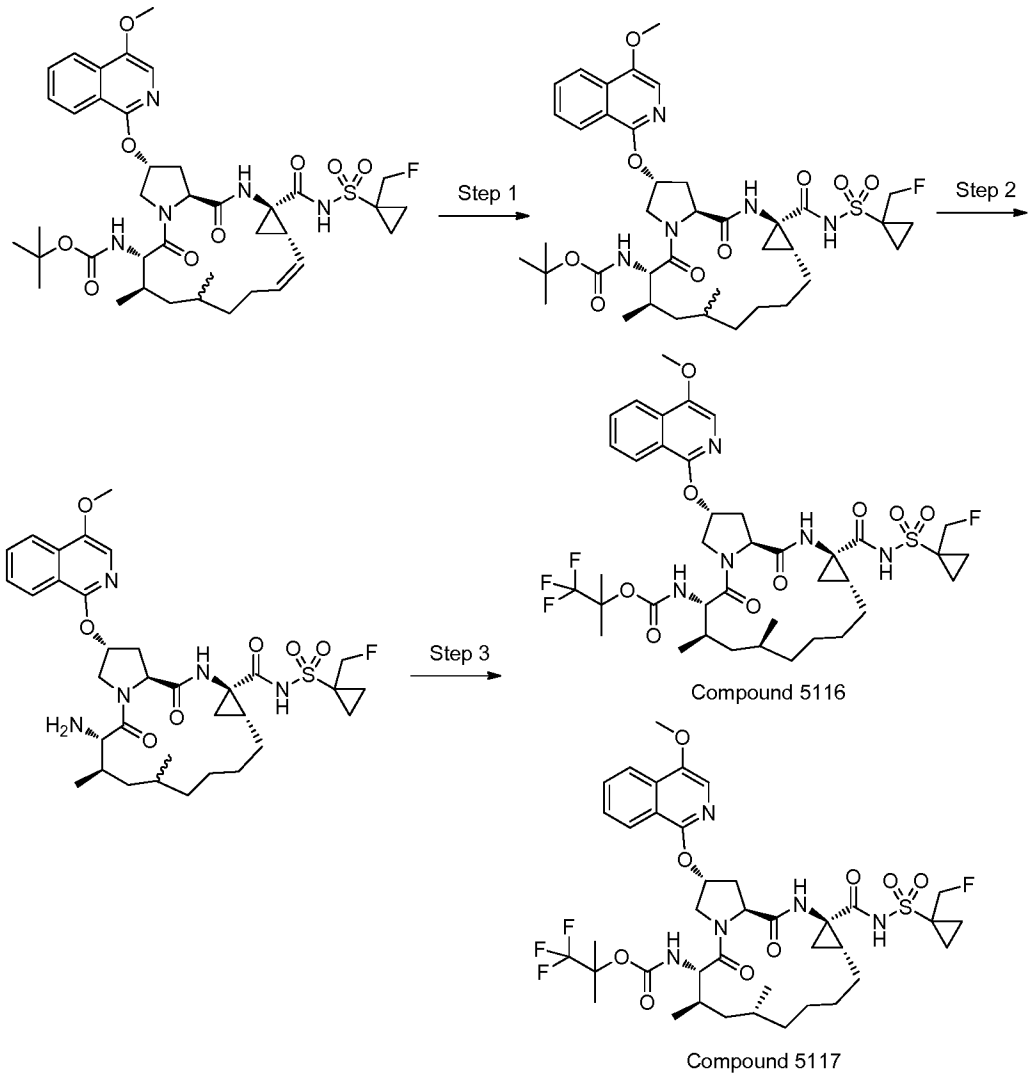
Compound 5351: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclobutylsulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. LC/MS: MS *m/z* $(M+H)^+$ 768.5.

Compound 5352: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclobutylsulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.01 (s, 1H), 8.11 (d, *J*=8.2 Hz, 1H), 8.06 (d, *J*=8.5 Hz, 1H), 7.79 (t, *J*=7.6 Hz, 1H), 7.65 (s, 1H), 7.59 (t, *J*=7.8 Hz, 1H), 7.18 (d, *J*=7.3 Hz, 1H), 5.76 (br. s., 1H), 5.52 (br. s., 1H), 5.00 (t, *J*=9.3 Hz, 1H), 4.60

(d, *J*=11.0 Hz, 1H), 4.49 - 4.41 (m, 1H), 4.22 (t, *J*=7.9 Hz, 1H), 3.98 (s, 3H), 3.93 - 3.88 (m, 1H), 3.75 - 3.67 (m, 1H), 3.18 (d, *J*=5.2 Hz, 1H), 2.73 - 2.58 (m, 2H), 2.41 - 2.14 (m, 7H), 2.01 - 1.00 (m, 17H), 0.93 (d, *J*=7.0 Hz, 3H), 0.88 (d, *J*=6.4 Hz, 3H), 0.72 (t, *J*=12.1 Hz, 1H); LC/MS: MS *m/z* $(M+H)^+$ 768.5.

Preparation of Compound 5116 and Compound 5117

Scheme



Step 1

A suspension of tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate

(220 mg, 0.280 mmol) and 5% Pt(S)/C (27.3 mg, 7.00 μmol) in AcOEt (5 mL)) was hydrogenated under a 50 PSI atmosphere of H2 for 1h. After filtration through a celite-containing plug washing with AcOEt, the filtrate was concentrated to give 220 mg of a crude product that will be used in the next step as it is. LC/MS: MS *m/z* $(M+H)^+$ 788.40.

Step 2

To a solution of tert-butyl ((2R,6S,7R,13aR,14aR,16aS)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate (240 mg, 0.305 mmol) in CH2Cl2 (1 mL) was added TFA (0.235 mL, 3.05 mmol). The resulting solution was stirred for 1h and concentrated to give 244 mg of a crude product as TFA salt that was used in the next step as it is. LC/MS: MS *m/z* $(M+H)^+$ 688.24.

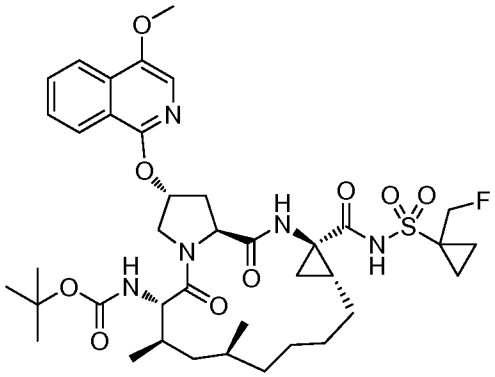
Step 3

A solution of (2R,6S,7R,13aR,14aR,16aS)-6-amino-N-((1-(fluoromethyl)cyclopropyl)sulfonyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide (34.4 mg, 0.05 mmol), pyridin-2-yl (1,1,1-trifluoro-2-methylpropan-2-yl) carbonate (14.95 mg, 0.060 mmol), and N-ethyl-N-isopropylpropan-2-amine (0.044 mL, 0.250 mmol) in CH2Cl2 (1 mL) was stirred for 16 h. After concentration, the residue was purified by prep HPLC to 9.3 mg of Compound 5116 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aR,14aR,16aS)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate as a solid and 11.3 mg of Compound 5117 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aR,14aR,16aS)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate as a solid.

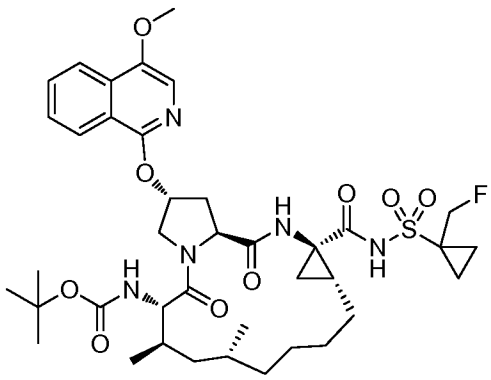
Compound 5116: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aR,14aR,16aS)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-

7,9-dimethyl-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 842.3 (M^++1).

Compound 5117: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aR,14aR,16aS)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.38 (s, 1H), 8.99 (br. s., 1H), 8.07 (d, *J*=8.5 Hz, 1H), 8.10 (d, *J*=8.2 Hz, 1H), 7.83 - 7.76 (m, 2H), 7.67 (s, 1H), 7.62 (t, *J*=7.6 Hz, 1H), 5.76 (br. s., 1H), 4.84 - 4.74 (d, *J*=11.3 Hz, 1H), 4.69 - 4.59 (d, *J*=11.3 Hz, 1H), 4.57 - 4.43 (m, 2H), 3.98 (s, 3H), 3.94 - 3.87 (m, 1H), 3.70 (dd, *J*=10.8, 8.1 Hz, 1H), 2.60 (d, *J*=7.0 Hz, 1H), 2.34 - 2.22 (m, 1H), 1.96 - 1.86 (m, 1H), 1.78 (d, *J*=6.4 Hz, 1H), 1.69 (d, *J*=12.2 Hz, 1H), 1.56 (br. s., 4H), 1.35 (s, 6H), 1.26 (s, 3H), 1.28 (s, 3H), 1.09 (s, 3H), 1.02 (d, *J*=11.6 Hz, 1H), 0.95 (d, *J*=6.7 Hz, 4H), 0.88 (d, *J*=6.1 Hz, 3H), 0.71 (t, *J*=12.2 Hz, 1H); MS:



Compound 5114



Compound 5115

MS *m/z* 842.3 (M^++1).

Preparation of Compound 5114 and Compoun 5115

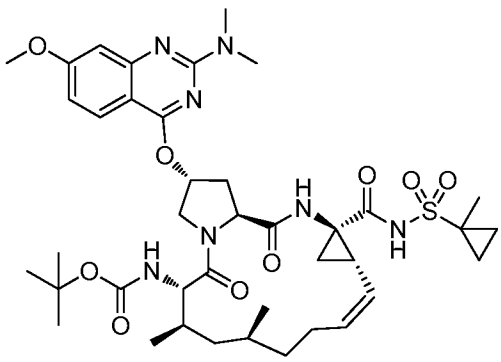
A suspension of tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate (15 mg, 0.019 mmol) and 5% Pt(S)/C (1.862 mg, 0.477 μmol) in AcOEt (5 mL)) was hydrogenated under a 50 PSI atomsophere of H2 for 1h. After filtration through a celite-containing plug washing with AcOEt, the filtrate was concentrated, the residue

was purified by prep HPLC to 0.4 mg of Compound 5114 tert-butyl ((2R,6S,7R,9S,13aR,14aR,16aS)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate as a solid and 9.9 mg of Compound 5115 tert-butyl ((2R,6S,7R,9R,13aR,14aR,16aS)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate as a solid, respectively.

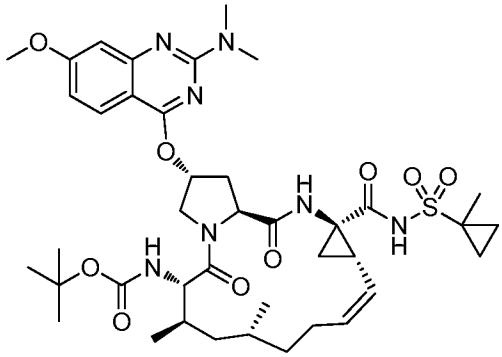
Compound 5114: tert-butyl ((2R,6S,7R,9S,13aR,14aR,16aS)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 788.4 (M^++1).

Compound 5115: tert-butyl ((2R,6S,7R,9R,13aR,14aR,16aS)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.38 (br. s., 1H), 8.96 (br. s., 1H), 8.12 (d, *J*=8.2 Hz, 1H), 8.06 (d, *J*=8.5 Hz, 1H), 7.79 (t, *J*=7.2 Hz, 1H), 7.68 - 7.63 (m, 1H), 7.59 (t, *J*=7.3 Hz, 1H), 7.14 (d, *J*=8.5 Hz, 1H), 5.76 (br. s., 1H), 4.79 - 4.65 (m, 1H), 4.59 (d, *J*=11.0 Hz, 1H), 4.47 - 4.36 (m, 1H), 3.98 (s, 3H), 3.94 - 3.86 (m, 1H), 3.76 - 3.65 (m, 1H), 2.64 - 2.56 (m, 1H), 2.27 (t, *J*=10.4 Hz, 1H), 1.92 (s, 1H), 1.76 (d, *J*=6.7 Hz, 1H), 1.69 (d, *J*=10.7 Hz, 1H), 1.62 (br. s., 1H), 1.56 (br. s., 2H), 1.38 (br. s., 1H), 1.31 (br. s., 3H), 1.29 - 1.20 (m, 6H), 1.15 (s, 8H), 1.07 - 0.98 (m, 2H), 0.95 (d, *J*=6.7 Hz, 4H), 0.88 (d, *J*=6.4 Hz, 3H), 0.79 (d, *J*=6.4 Hz, 1H), 0.73 - 0.64 (m, 1H); MS: MS *m/z* 788.5 (M^++1).

Preparation of Compound 3001 and Compound 3002



Compound 3001



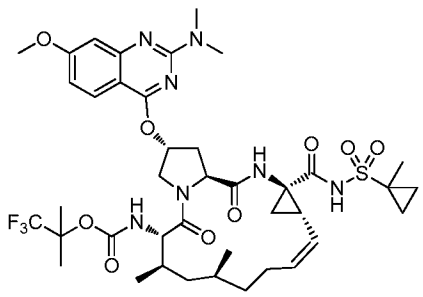
Compound 3002

Compound 3001 and Compound 3002 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

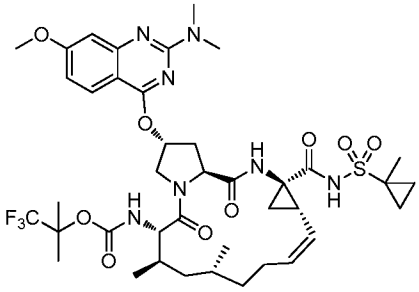
Compound 3001: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2-(dimethylamino)-7-methoxyquinazolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 812.5 (M^++1).

Compound 3002: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2-(dimethylamino)-7-methoxyquinazolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.10 (br. s., 1H), 7.72 (d, *J*=8.9 Hz, 1H), 7.22 (d, *J*=7.9 Hz, 1H), 6.82 (d, *J*=2.1 Hz, 1H), 6.65 (dd, *J*=8.9, 2.4 Hz, 1H), 5.81 (br. s., 1H), 5.59 - 5.47 (m, 1H), 5.04 - 4.93 (m, 1H), 4.57 (d, *J*=10.7 Hz, 1H), 4.45 (t, *J*=8.5 Hz, 1H), 3.97 - 3.90 (m, 1H), 3.85 (s, 3H), 3.73 (dd, *J*=10.5, 8.4 Hz, 1H), 3.24 - 3.16 (m, 6H), 2.75 - 2.58 (m, 2H), 2.41 - 2.24 (m, 2H), 1.98 - 0.67 (m, 31H); MS: MS *m/z* 812.5 (M^++1).

Preparation of Compound 3003 and Compound 3004



Compound 3003



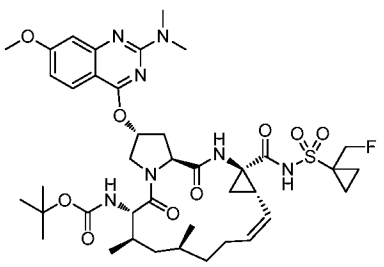
Compound 3004

Compound 3003 and Compound 3004 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

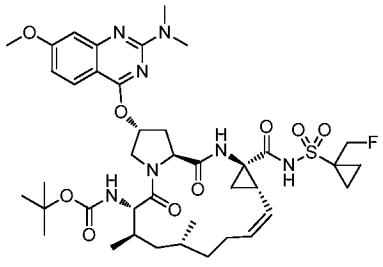
Compound 3003: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2-(dimethylamino)-7-methoxyquinazolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 866.5 (M^++1).

Compound 3004: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2-(dimethylamino)-7-methoxyquinazolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.13 (br. s., 1H), 7.87 (d, *J*=7.9 Hz, 1H), 7.69 (d, *J*=9.2 Hz, 1H), 6.83 (d, *J*=2.4 Hz, 1H), 6.69 (dd, *J*=8.9, 2.4 Hz, 1H), 5.81 (br. s., 1H), 5.58 - 5.47 (m, 1H), 5.03 - 4.92 (m, 1H), 4.60 - 4.42 (m, 2H), 3.98 - 3.89 (m, 1H), 3.85 (s, 3H), 3.72 (dd, *J*=10.7, 7.9 Hz, 1H), 3.25 - 3.14 (m, 6H), 2.72 - 2.58 (m, 2H), 2.39 - 2.24 (m, 2H), 1.96 - 1.78 (m, 2H), 1.74 - 0.70 (m, 26H); MS: MS *m/z* 866.5 (M^++1).

Preparation of Compound 3005 and Compound 3006



Compound 3005



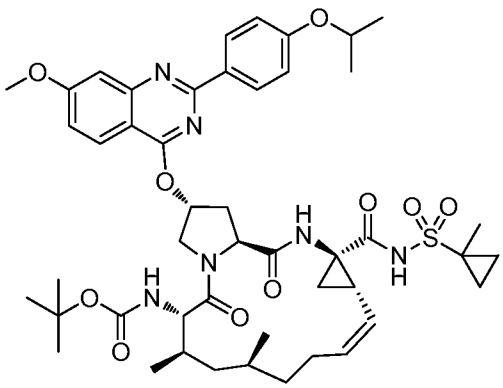
Compound 3006

Compound 3005 and Compound 3006 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

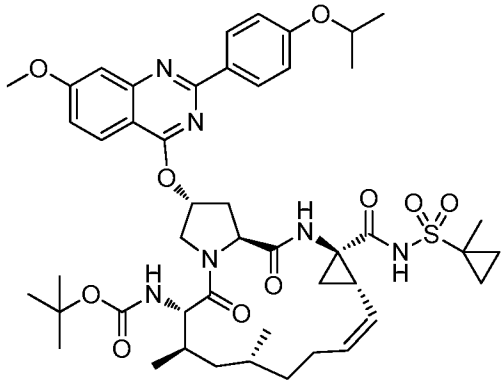
Compound 3005: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2-(dimethylamino)-7-methoxyquinazolin-4-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 830.5 (M^++1).

Compound 3006: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2-(dimethylamino)-7-methoxyquinazolin-4-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (s, 1H), 9.01 (br. s., 1H), 7.72 (d, *J*=8.9 Hz, 1H), 7.22 (d, *J*=7.9 Hz, 1H), 6.83 (d, *J*=2.4 Hz, 1H), 6.65 (dd, *J*=8.9, 2.4 Hz, 1H), 5.80 (br. s., 1H), 5.58 - 5.44 (m, 1H), 5.00 (t, *J*=9.6 Hz, 1H), 4.88 - 4.72 (m, 1H), 4.65 - 4.46 (m, 2H), 4.42 (t, *J*=8.1 Hz, 1H), 3.98 - 3.89 (m, 1H), 3.85 (s, 3H), 3.73 (dd, *J*=10.4, 8.5 Hz, 1H), 3.21 (s, 6H), 2.72 - 2.58 (m, 2H), 2.36 - 2.22 (m, 2H), 1.97 - 1.76 (m, 2H), 1.73 - 0.66 (m, 26H); MS: MS *m/z* 830.5 (M^++1).

Preparation of Compound 3007 and Compound 3008



Compound 3007



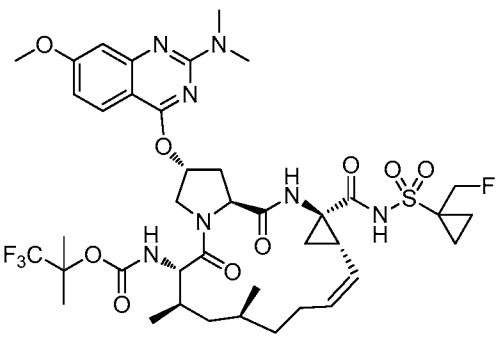
Compound 3008

Compound 3007 and Compound 3008 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

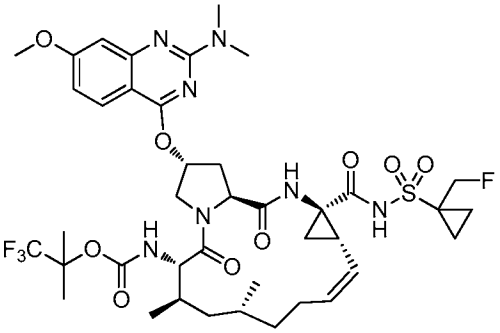
Compound 3007: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2-(4-isopropoxyphenyl)-7-methoxyquinazolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 903.5 (M^++1).

Compound 3008: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2-(4-isopropoxyphenyl)-7-methoxyquinazolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.07 (s, 1H), 9.11 (s, 1H), 8.51 - 8.41 (m, 2H), 7.98 (d, *J*=9.2 Hz, 1H), 7.32 (d, *J*=2.4 Hz, 1H), 7.22 (d, *J*=7.9 Hz, 1H), 7.14 - 7.04 (m, 3H), 6.06 (br. s., 1H), 5.60 - 5.48 (m, 1H), 4.99 (t, *J*=9.8 Hz, 1H), 4.83 - 4.72 (m, 1H), 4.69 (d, *J*=12.2 Hz, 1H), 4.53 (dd, *J*=9.3, 7.5 Hz, 1H), 4.02 - 3.93 (m, 4H), 3.70 (dd, *J*=10.7, 8.2 Hz, 1H), 2.78 - 2.61 (m, 2H), 2.46 - 2.24 (m, 2H), 1.97 - 1.76 (m, 2H), 1.74 - 1.65 (m, 1H), 1.65 - 1.58 (m, 1H), 1.57 - 1.50 (m, 1H), 1.49 - 0.69 (m, 32H); MS: MS *m/z* 903.5 (M^++1).

Preparation of Compound 3009 and Compound 3010



Compound 3009



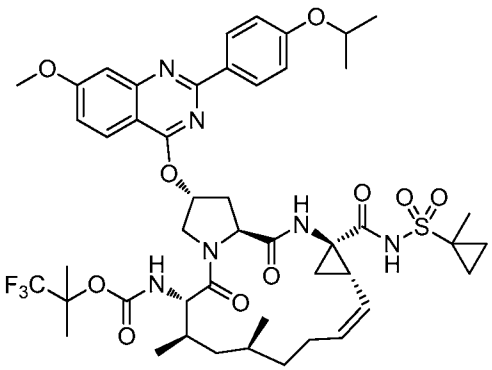
Compound 3010

Compound 3009 and Compound 3010 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

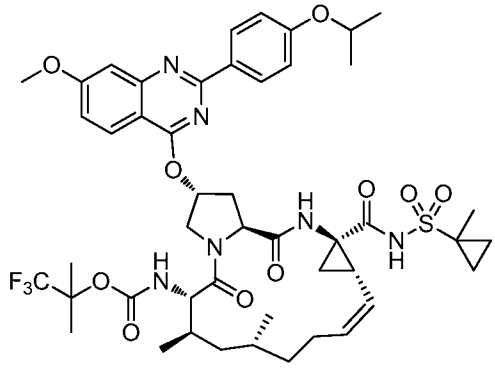
Compound 3009: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2-(dimethylamino)-7-methoxyquinazolin-4-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 884.4 (M^++1).

Compound 3010: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2-(dimethylamino)-7-methoxyquinazolin-4-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (br. s, 1H), 9.04 (br. s., 1H), 7.86 (d, *J*=7.9 Hz, 1H), 7.69 (d, *J*=8.9 Hz, 1H), 6.84 (d, *J*=2.4 Hz, 1H), 6.69 (dd, *J*=8.9, 2.4 Hz, 1H), 5.81 (br. s., 1H), 5.56 - 5.47 (m, 1H), 5.01 (t, *J*=9.8 Hz, 1H), 4.88 - 4.72 (m, 1H), 4.63 - 4.42 (m, 3H), 3.97 - 3.90 (m, 1H), 3.72 (dd, *J*=10.8, 8.1 Hz, 1H), 3.21 (s, 6H), 2.70 - 2.59 (m, 2H), 2.41 - 2.23 (m, 2H), 1.96 - 1.80 (m, 2H), 1.73 - 1.64 (m, 1H), 1.61 - 1.08 (m, 18H), 0.93 (d, *J*=7.0 Hz, 3H), 0.90 (d, *J*=6.1 Hz, 3H), 0.75 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 884.4 (M^++1).

Preparation of Compound 3011 and Compound 3012



Compound 3011



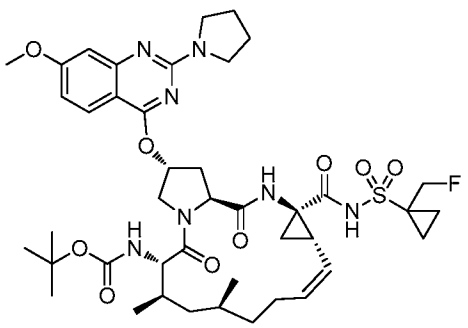
Compound 3012

Compounds 3011 and 3012 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

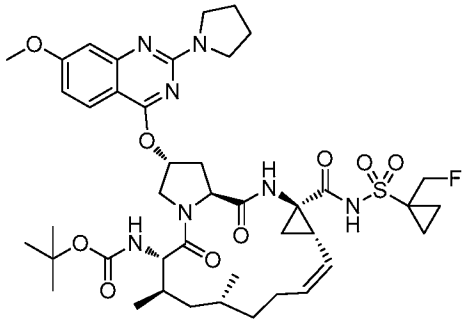
Compound 3011: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2-(4-isopropoxyphenyl)-7-methoxyquinazolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 957.5 (M^++1).

Compound 3012: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2-(4-isopropoxyphenyl)-7-methoxyquinazolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (br. s., 1H), 9.14 (br. s., 1H), 8.47 (d, *J*=8.9 Hz, 2H), 7.95 (d, *J*=9.2 Hz, 1H), 7.33 (d, *J*=2.4 Hz, 1H), 7.14 (dd, *J*=8.9, 2.4 Hz, 1H), 7.09 (d, *J*=8.9 Hz, 2H), 6.06 (br. s., 1H), 5.60 - 5.47 (m, 1H), 5.06 - 4.94 (m, 1H), 4.82 - 4.71 (m, 1H), 4.68 - 4.48 (m, 2H), 4.03 - 3.98 (m, 1H), 3.96 (s, 3H), 3.69 (dd, *J*=10.5, 8.1 Hz, 1H), 2.79 - 2.63 (m, 2H), 2.46 - 2.26 (m, 2H), 1.97 - 1.79 (m, 2H), 1.76 - 0.69 (m, 33H); MS: MS *m/z* 957.5 (M^++1).

Preparation of Compound 3013 and Compound 3014



Compound 3013



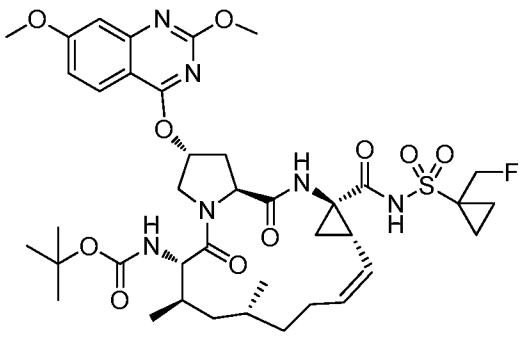
Compound 3014

Compounds 3013 and 3014 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 3013: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((7-methoxy-2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 856.4 (M^++1).

Compound 3014: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((7-methoxy-2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (br. s., 1H), 9.02 (br. s., 1H), 7.72 (d, *J*=8.9 Hz, 1H), 7.21 (d, *J*=7.3 Hz, 1H), 6.82 (d, *J*=2.1 Hz, 1H), 6.64 (dd, *J*=9.0, 2.3 Hz, 1H), 5.78 (br. s., 1H), 5.57 - 5.45 (m, 1H), 5.08 - 4.93 (m, 1H), 4.90 - 4.69 (m, 1H), 4.65 - 4.38 (m, 3H), 3.95 (dd, *J*=11.4, 3.5 Hz, 1H), 3.85 (s, 3H), 3.74 (dd, *J*=10.7, 8.5 Hz, 1H), 3.58 (br. s., 4H), 2.72 - 2.59 (m, 2H), 2.35 - 2.24 (m, 2H), 2.02 - 1.07 (m, 25H), 0.93 (d, *J*=7.0 Hz, 3H), 0.89 (d, *J*=6.1 Hz, 3H), 0.73 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 856.4 (M^++1).

Preparation of Compound 3015

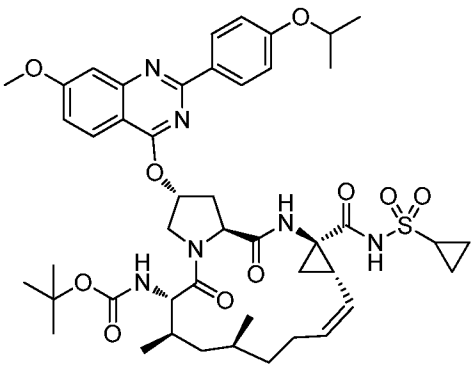


Compound 3015

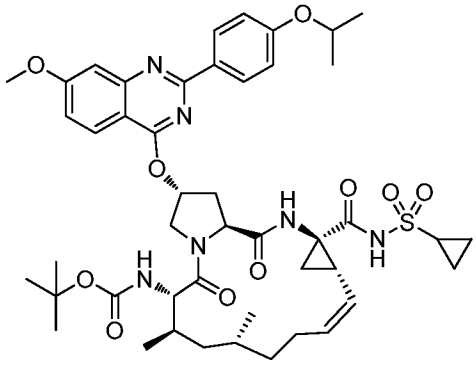
Compound 3015 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 3015: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,7-dimethoxyquinazolin-4-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (br. s., 1H), 9.04 (br. s., 1H), 7.88 (d, *J*=9.2 Hz, 1H), 7.19 (br. s., 1H), 7.11 (d, *J*=2.1 Hz, 1H), 6.96 (dd, *J*=9.0, 2.3 Hz, 1H), 5.79 (br. s., 1H), 5.58 - 5.45 (m, 1H), 5.09 - 4.95 (m, 1H), 4.89 - 4.72 (m, 1H), 4.70 - 4.40 (m, 3H), 3.98 (s, 3H), 3.94 - 3.87 (m, 4H), 3.67 (dd, *J*=10.7, 8.2 Hz, 1H), 2.72 - 2.59 (m, 2H), 2.41 - 2.22 (m, 2H), 1.95 - 0.66 (m, 28H); MS: MS *m/z* 817.4 (M^++1).

Preparation of Compound 3016 and Compound 3017



Compound 3016



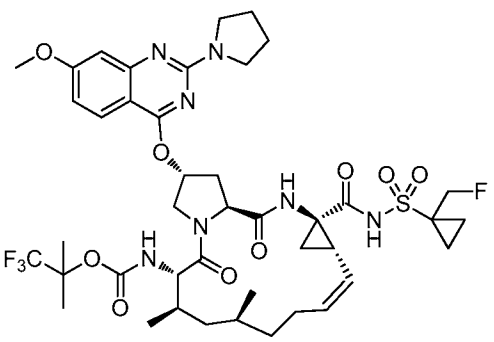
Compound 3017

Compounds 3016 and 3017 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

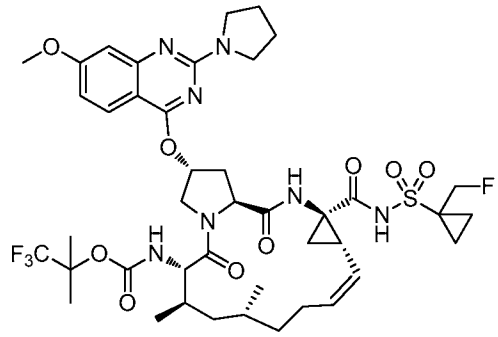
Compound 3016: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2-(4-isopropoxyphenyl)-7-methoxyquinazolin-4-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 889.5 (M^++1).

Compound 3017: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2-(4-isopropoxyphenyl)-7-methoxyquinazolin-4-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.22 (br. s., 1H), 8.97 (br. s., 1H), 8.47 (d, *J*=8.9 Hz, 2H), 7.98 (d, *J*=8.9 Hz, 1H), 7.32 (d, *J*=2.1 Hz, 1H), 7.21 (d, *J*=7.6 Hz, 1H), 7.13 - 7.04 (m, 3H), 6.03 (br. s., 1H), 5.59 - 5.46 (m, 1H), 5.14 - 5.02 (m, 1H), 4.76 (spt, *J*=6.0 Hz, 1H), 4.67 (d, *J*=11.6 Hz, 1H), 4.48 (t, *J*=8.5 Hz, 1H), 4.02 - 3.93 (m, 4H), 3.70 (dd, *J*=10.7, 8.2 Hz, 1H), 2.99 - 2.87 (m, 1H), 2.79 - 2.62 (m, 2H), 2.45 - 2.36 (m, 1H), 2.34 - 2.21 (m, 1H), 1.98 - 0.65 (m, 34H); MS: MS *m/z* 889.5 (M^++1).

Preparation of Compound 3018 and Compound 3019



Compound 3018



Compound 3019

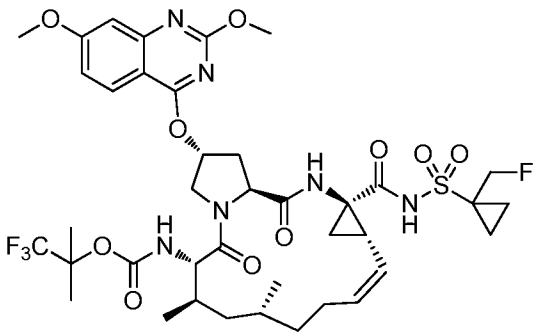
Compounds 3018 and 3019 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 3018: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((7-methoxy-2-(pyrrolidin-1-

yl)quinazolin-4-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 910.4 (M^++1).

Compound 3019: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((7-methoxy-2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.26 (br. s., 1H), 9.03 (br. s., 1H), 7.86 (d, *J*=7.9 Hz, 1H), 7.69 (d, *J*=8.9 Hz, 1H), 6.83 (d, *J*=2.4 Hz, 1H), 6.67 (dd, *J*=8.9, 2.4 Hz, 1H), 5.79 (br. s., 1H), 5.58 - 5.45 (m, 1H), 5.03 (br. s., 1H), 4.89 - 4.70 (m, 1H), 4.65 - 4.42 (m, 3H), 3.94 (dd, *J*=11.6, 3.4 Hz, 1H), 3.85 (s, 3H), 3.73 (dd, *J*=10.7, 8.2 Hz, 1H), 3.59 (br. s., 4H), 2.68 - 2.57 (m, 2H), 2.37 - 2.22 (m, 2H), 2.02 - 1.09 (m, 22H), 0.94 (d, *J*=6.7 Hz, 3H), 0.90 (d, *J*=6.4 Hz, 3H), 0.75 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 910.4 (M^++1).

Preparation of Compound 3020



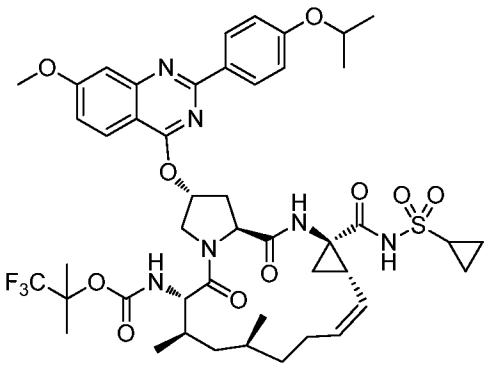
Compound 3020

Compound 3020 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

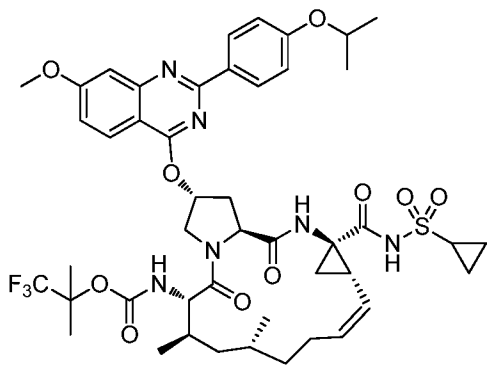
Compound 3020: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,7-dimethoxyquinazolin-4-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 8.41 (br. s., 1H), 7.86 (d, *J*=8.9 Hz, 1H), 7.78 (d, *J*=7.9 Hz, 1H), 7.11 (d, *J*=2.4 Hz, 1H),

6.99 (dd, *J*=9.2, 2.4 Hz, 1H), 5.77 (br. s., 1H), 5.51 (t, *J*=9.6 Hz, 1H), 5.35 (td, *J*=10.1, 5.8 Hz, 1H), 4.70 (s, 1H), 4.60 (s, 1H), 4.53 (d, *J*=11.3 Hz, 1H), 4.44 (dd, *J*=9.5, 7.3 Hz, 1H), 3.98 (s, 3H), 3.91 (s, 3H), 3.87 (dd, *J*=11.4, 3.2 Hz, 1H), 3.66 (dd, *J*=10.5, 8.1 Hz, 1H), 2.51 - 2.46 (m, 1H), 2.40 - 2.18 (m, 3H), 1.89 - 1.75 (m, 3H), 1.43 (dd, *J*=8.1, 3.8 Hz, 1H), 1.38 - 1.17 (m, 12H), 1.05 (s, 3H), 0.92 (d, *J*=7.0 Hz, 3H), 0.90 - 0.82 (m, 5H), 0.66 (t, *J*=11.3 Hz, 1H); MS: MS *m/z* 871.4 (M^++1).

Preparation of Compound 3021 and Compound 3022



Compound 3021



Compound 3022

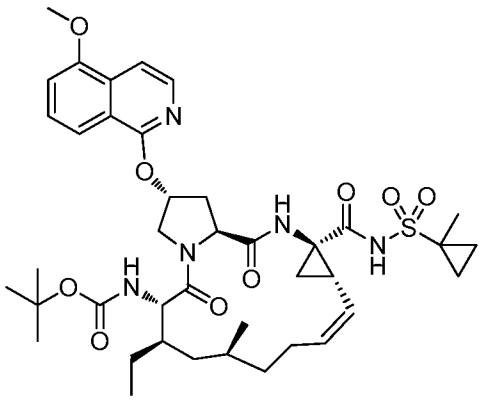
Compounds 3021 and 3022 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 3021: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2-(4-isopropoxyphenyl)-7-methoxyquinazolin-4-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 943.5 (M^++1).

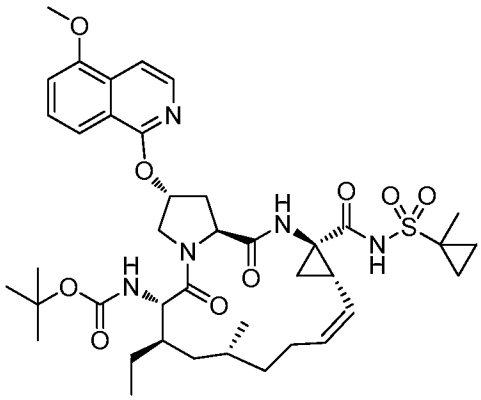
Compound 3022: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2-(4-isopropoxyphenyl)-7-methoxyquinazolin-4-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (br. s., 1H), 9.00 (br. s., 1H), 8.47 (d, *J*=8.9 Hz, 2H), 7.95 (d, *J*=8.9 Hz, 1H), 7.85 (d, *J*=7.3 Hz, 1H), 7.33 (d, *J*=2.4 Hz, 1H), 7.14 (dd, *J*=8.9, 2.4 Hz, 1H), 7.09 (d, *J*=9.2 Hz, 2H), 6.04 (br. s., 1H), 5.61 - 5.46 (m, 1H), 5.18 - 5.01 (m, 1H), 4.76 (spt, *J*=6.1 Hz, 1H), 4.61 (d, *J*=11.3 Hz, 1H), 4.52 (t, *J*=8.5 Hz, 1H), 4.01 - 3.93 (m, 4H),

3.69 (dd, *J*=10.7, 7.6 Hz, 1H), 3.00 - 2.86 (m, 1H), 2.80 - 2.60 (m, 2H), 2.47 - 2.36 (m, 1H), 2.29 (d, *J*=12.8 Hz, 1H), 1.99 - 0.67 (m, 31H); MS: MS *m/z* 943.5 (M^++1).

Preparation of Compound 3023 and Compound 3024



Compound 3023



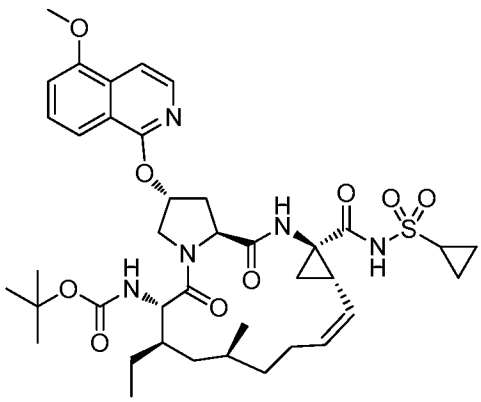
Compound 3024

Compounds 3023 and 3024 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

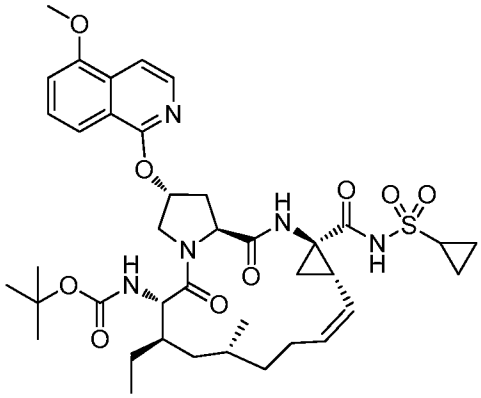
Compound 3023: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((5-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 782.4 (M^++1).

Compound 3024: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((5-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.10 (br. s., 1H), 8.03 (d, *J*=6.1 Hz, 1H), 7.69 (d, *J*=8.2 Hz, 1H), 7.54 (d, *J*=5.8 Hz, 1H), 7.46 (t, *J*=8.1 Hz, 1H), 7.25 - 7.17 (m, 2H), 5.84 (br. s., 1H), 5.59 - 5.46 (m, *J*=4.6 Hz, 1H), 4.98 (t, *J*=9.6 Hz, 1H), 4.63 (d, *J*=11.0 Hz, 1H), 4.53 - 4.43 (m, 1H), 4.01 - 3.89 (m, 5H), 2.77 - 2.58 (m, 2H), 2.41 - 2.24 (m, 2H), 2.01 - 0.67 (m, 33H); MS: MS *m/z* 782.5 (M^++1).

Preparation of Compound 3025 and Compound 3026



Compound 3025



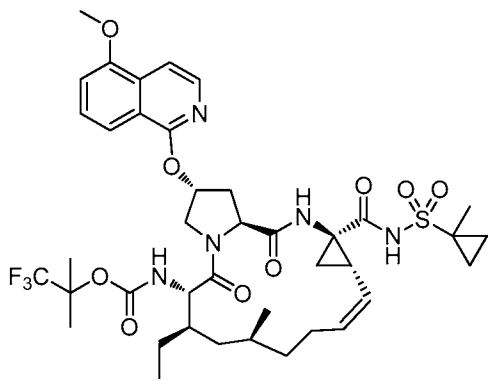
Compound 3026

Compounds 3025 and 3026 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

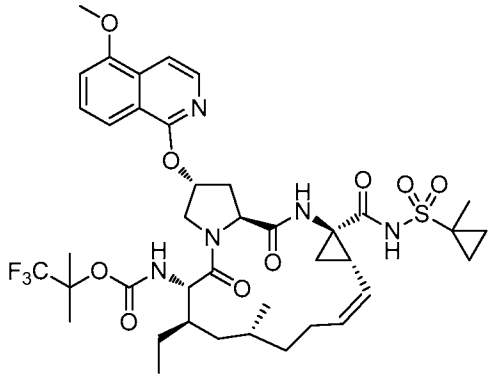
Compound 3025: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((5-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 768.4 (M^++1).

Compound 3026: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((5-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.97 (s, 1H), 8.03 (d, *J*=6.1 Hz, 1H), 7.69 (d, *J*=8.2 Hz, 1H), 7.54 (d, *J*=6.1 Hz, 1H), 7.46 (t, *J*=8.1 Hz, 1H), 7.25 - 7.17 (m, 2H), 5.83 (br. s., 1H), 5.58 - 5.48 (m, 1H), 5.05 (t, *J*=9.9 Hz, 1H), 4.63 (d, *J*=11.6 Hz, 1H), 4.50 - 4.41 (m, 1H), 4.02 - 3.87 (m, 5H), 2.97 - 2.87 (m, 1H), 2.77 - 2.59 (m, 2H), 2.40 - 2.24 (m, 2H), 2.01 - 1.85 (m, 2H), 1.67 - 0.67 (m, 28H); MS: MS *m/z* 768.4 (M^++1).

Preparation of Compound 3027 and Compound 3028



Compound 3027



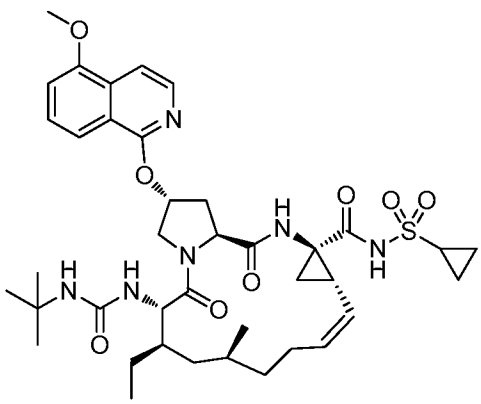
Compound 3028

Compounds 3027 and 3028 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

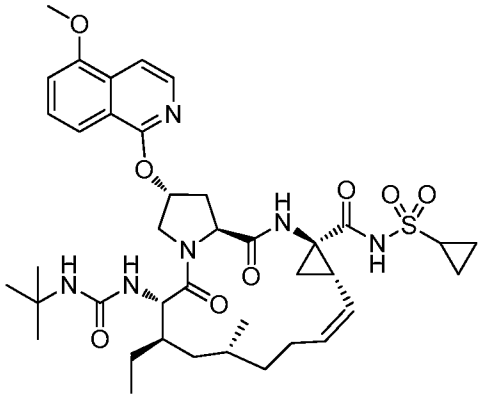
Compound 3027: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((5-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 836.4 (M^++1).

Compound 3028: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((5-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.13 (br. s., 1H), 8.04 (d, *J*=6.1 Hz, 1H), 7.86 (d, *J*=8.5 Hz, 1H), 7.67 (d, *J*=8.2 Hz, 1H), 7.55 (d, *J*=5.8 Hz, 1H), 7.49 (t, *J*=8.1 Hz, 1H), 7.24 (d, *J*=7.6 Hz, 1H), 5.85 (br. s., 1H), 5.59 - 5.47 (m, 1H), 5.05 - 4.91 (m, 1H), 4.62 - 4.47 (m, 2H), 4.01 - 3.86 (m, 5H), 2.76 - 2.59 (m, 2H), 2.42 - 2.26 (m, 2H), 2.02 - 1.85 (m, 2H), 1.68 - 0.68 (m, 28H); MS: MS *m/z* 836.4 (M^++1).

Preparation of Compound 3029 and Compound 3030



Compound 3029



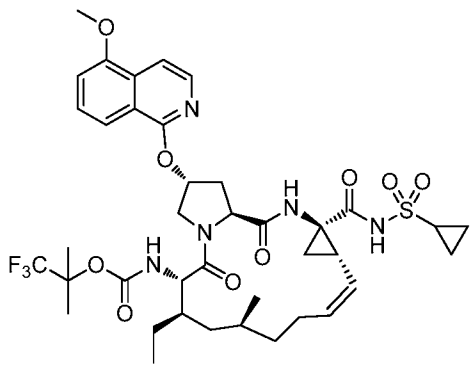
Compound 3030

Compounds 3029 and 3030 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

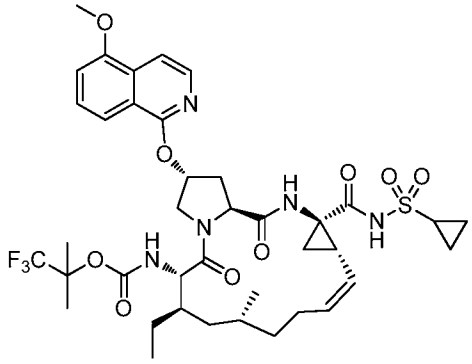
Compound 3029: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-N-(cyclopropylsulfonyl)-7-ethyl-2-((5-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide; MS: MS *m/z* 767.4 (M^++1).

Compound 3030: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-N-(cyclopropylsulfonyl)-7-ethyl-2-((5-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (br. s., 1H), 8.93 (br. s., 1H), 8.03 (d, *J*=6.1 Hz, 1H), 7.70 (d, *J*=8.5 Hz, 1H), 7.54 (d, *J*=6.1 Hz, 1H), 7.44 (t, *J*=8.1 Hz, 1H), 7.23 (d, *J*=7.9 Hz, 1H), 5.96 (d, *J*=9.2 Hz, 1H), 5.88 - 5.79 (m, 1H), 5.56 - 5.46 (m, 1H), 5.12 - 5.00 (m, 1H), 4.63 (d, *J*=10.4 Hz, 1H), 4.40 (dd, *J*=9.9, 7.2 Hz, 1H), 4.07 (t, *J*=10.2 Hz, 1H), 3.98 (s, 3H), 3.95 - 3.87 (m, 1H), 2.91 (s, 1H), 2.79 - 2.57 (m, 2H), 2.41 - 2.24 (m, 2H), 2.00 - 0.69 (m, 31H); MS: MS *m/z* 767.4 (M^++1).

Preparation of Compound 3031 and Compound 3032



Compound 3031



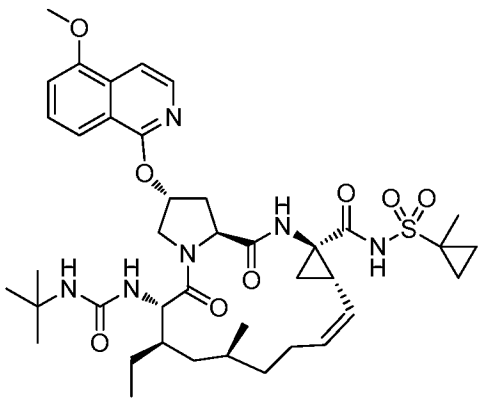
Compound 3032

Compounds 3031 and 3032 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

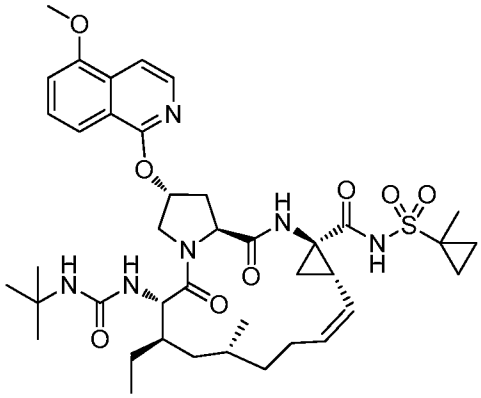
Compound 3031: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((5-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 822.4 (M^++1).

Compound 3032: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((5-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (s, 1H), 9.01 (s, 1H), 8.04 (d, *J*=6.1 Hz, 1H), 7.86 (d, *J*=8.2 Hz, 1H), 7.67 (d, *J*=8.5 Hz, 1H), 7.55 (d, *J*=5.8 Hz, 1H), 7.49 (t, *J*=8.1 Hz, 1H), 7.24 (d, *J*=7.9 Hz, 1H), 5.84 (br. s., 1H), 5.60 - 5.47 (m, 1H), 5.06 (t, *J*=9.8 Hz, 1H), 4.56 (d, *J*=11.6 Hz, 1H), 4.52 - 4.45 (m, 1H), 3.98 (s, 3H), 3.95 - 3.86 (m, 2H), 2.97 - 2.88 (m, 1H), 2.72 - 2.61 (m, 2H), 2.40 - 2.25 (m, 2H), 2.01 - 1.86 (m, 2H), 1.67 - 0.67 (m, 25H); MS: MS *m/z* 822.4 (M^++1).

Preparation of Compound 3033 and Compound 3034



Compound 3033



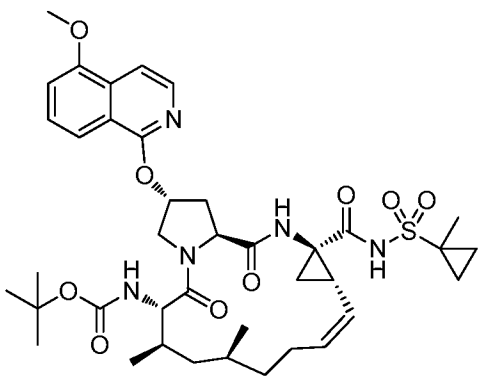
Compound 3034

Compounds 3033 and 3034 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

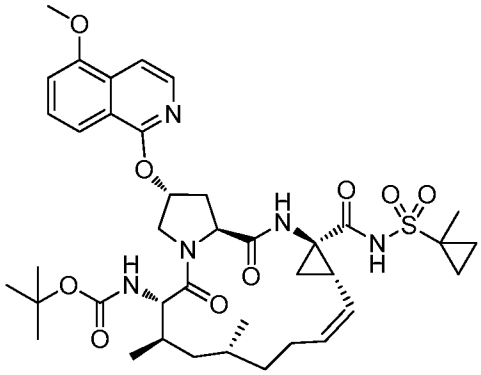
Compound 3033: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-7-ethyl-2-((5-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide; MS: MS *m/z* 781.5 (M^++1).

Compound 3034: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-7-ethyl-2-((5-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.06 (br. s., 1H), 8.02 (d, *J*=5.8 Hz, 1H), 7.70 (d, *J*=8.5 Hz, 1H), 7.54 (d, *J*=6.1 Hz, 1H), 7.45 (t, *J*=8.1 Hz, 1H), 7.23 (d, *J*=7.6 Hz, 1H), 5.96 (d, *J*=9.2 Hz, 1H), 5.84 (br. s., 1H), 5.56 - 5.47 (m, 1H), 4.98 (t, *J*=10.1 Hz, 1H), 4.64 (d, *J*=10.7 Hz, 1H), 4.48 - 4.39 (m, 1H), 4.07 (t, *J*=10.1 Hz, 1H), 4.01 - 3.89 (m, 4H), 2.80 - 2.69 (m, 1H), 2.68 - 2.57 (m, 1H), 2.42 - 2.24 (m, 2H), 1.98 - 1.85 (m, 1H), 1.76 (br. s., 1H), 1.66 - 0.73 (m, 32H); MS: MS *m/z* 781.4 (M^++1).

Preparation of Compound 3035 and Compound 3036



Compound 3035



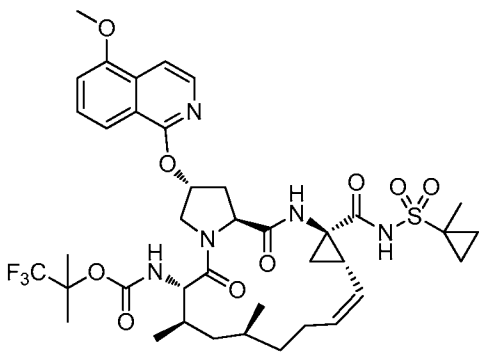
Compound 3036

Compounds 3035 and 3036 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

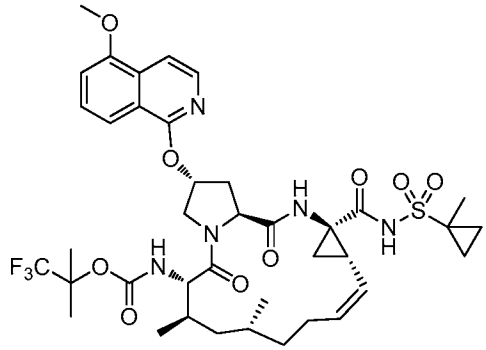
Compound 3035: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 768.4 (M^++1).

Compound 3036: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.10 (br. s., 1H), 8.02 (d, *J*=6.1 Hz, 1H), 7.71 (d, *J*=7.9 Hz, 1H), 7.53 (d, *J*=5.8 Hz, 1H), 7.46 (t, *J*=8.1 Hz, 1H), 7.23 (d, *J*=7.9 Hz, 1H), 7.18 (d, *J*=7.9 Hz, 1H), 5.83 (br. s., 1H), 5.58 - 5.47 (m, 1H), 5.09 - 4.90 (m, 1H), 4.61 (d, *J*=11.9 Hz, 1H), 4.52 - 4.45 (m, 1H), 4.04 - 3.88 (m, 4H), 3.72 (t, *J*=9.5 Hz, 1H), 2.79 - 2.56 (m, 2H), 2.40 - 2.24 (m, 2H), 1.99 - 0.63 (m, 31H); MS: MS *m/z* 768.4 (M^++1).

Preparation of Compound 3037 and Compound 3038



Compound 3037



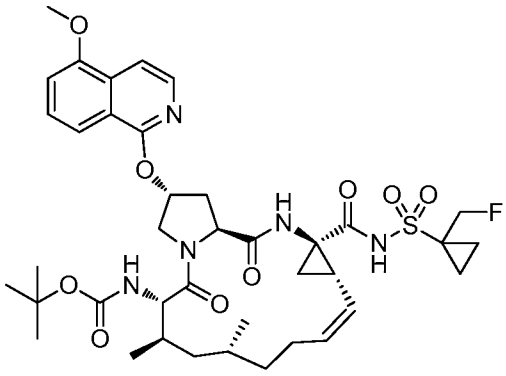
Compound 3038

Compounds 3037 and 3038 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 3037: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 822.4 (M^++1).

Compound 3038: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.14 (s, 1H), 8.03 (d, *J*=5.8 Hz, 1H), 7.83 (d, *J*=7.9 Hz, 1H), 7.69 (d, *J*=8.2 Hz, 1H), 7.54 (d, *J*=5.8 Hz, 1H), 7.49 (t, *J*=8.1 Hz, 1H), 7.24 (d, *J*=7.9 Hz, 1H), 5.84 (br. s., 1H), 5.54 (td, *J*=10.1, 6.1 Hz, 1H), 4.98 (t, *J*=9.9 Hz, 1H), 4.61 - 4.49 (m, 2H), 3.98 (s, 3H), 3.96 - 3.90 (m, 1H), 3.71 (dd, *J*=10.7, 7.9 Hz, 1H), 2.73 - 2.60 (m, 2H), 2.40 - 2.26 (m, 2H), 1.96 - 1.79 (m, 2H), 1.70 (dd, *J*=12.8, 7.3 Hz, 1H), 1.62 (dd, *J*=8.2, 5.2 Hz, 1H), 1.52 (dd, *J*=9.3, 5.3 Hz, 1H), 1.48 - 0.84 (m, 22H), 0.76 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 822.4 (M^++1).

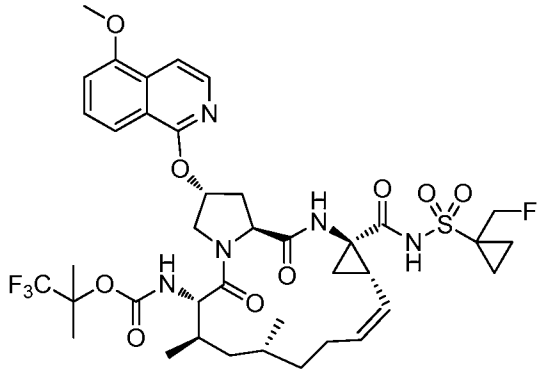
Preparation of Compound 3039



Compound 3039

Compound 3039 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117: Compound 3039: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (s, 1H), 9.02 (br. s., 1H), 8.03 (d, *J*=6.1 Hz, 1H), 7.72 (d, *J*=8.2 Hz, 1H), 7.54 (d, *J*=5.8 Hz, 1H), 7.46 (t, *J*=8.1 Hz, 1H), 7.23 (d, *J*=7.9 Hz, 1H), 7.19 (d, *J*=7.9 Hz, 1H), 5.82 (br. s., 1H), 5.58 - 5.47 (m, 1H), 5.07 - 4.95 (m, 1H), 4.91 - 4.73 (m, 1H), 4.67 - 4.40 (m, 3H), 3.98 (s, 3H), 3.95 - 3.89 (m, 1H), 3.73 (dd, *J*=10.5, 8.4 Hz, 1H), 2.73 - 2.57 (m, 2H), 2.36 - 2.24 (m, 2H), 1.96 - 1.75 (m, 2H), 1.69 (br. s., 1H), 1.60 - 0.83 (m, 24H), 0.73 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 786.4 (M^++1).

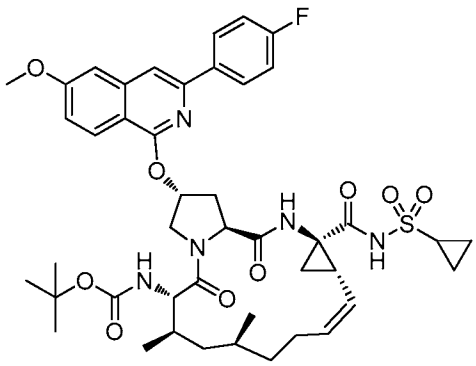
Preparation of Compound 3040



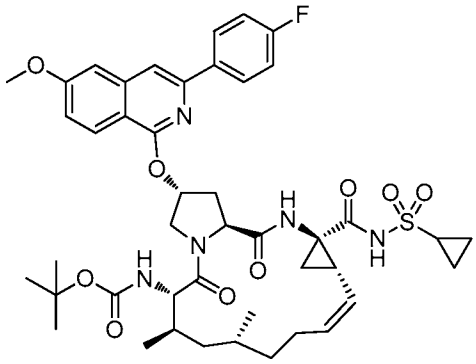
Compound 3040

Compound 3040 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117: Compound 3040: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.06 (s, 1H), 8.04 (d, *J*=5.8 Hz, 1H), 7.84 (d, *J*=7.9 Hz, 1H), 7.69 (d, *J*=8.2 Hz, 1H), 7.54 (d, *J*=6.1 Hz, 1H), 7.49 (t, *J*=7.9 Hz, 1H), 7.24 (d, *J*=7.9 Hz, 1H), 5.83 (br. s., 1H), 5.57 - 5.46 (m, 1H), 5.00 (t, *J*=10.1 Hz, 1H), 4.92 - 4.71 (m, 1H), 4.65 - 4.44 (m, 3H), 3.98 (s, 3H), 3.95 - 3.89 (m, 1H), 3.71 (dd, *J*=10.8, 8.1 Hz, 1H), 2.71 - 2.59 (m, 2H), 2.42 - 2.25 (m, 2H), 1.96 - 1.79 (m, 2H), 1.75 - 1.03 (m, 16H), 0.99 - 0.85 (m, 6H), 0.75 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 840.4 (M^++1).

Preparation of Compound 3041 and Compound 3042



Compound 3041



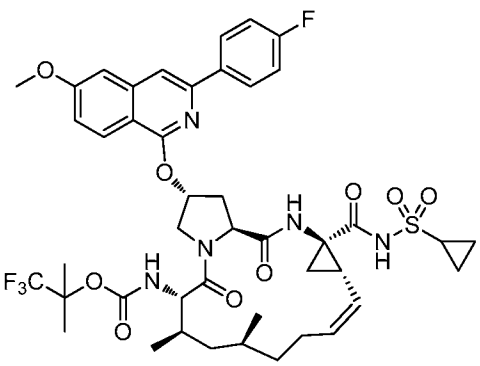
Compound 3042

Compounds 3041 and 3042 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

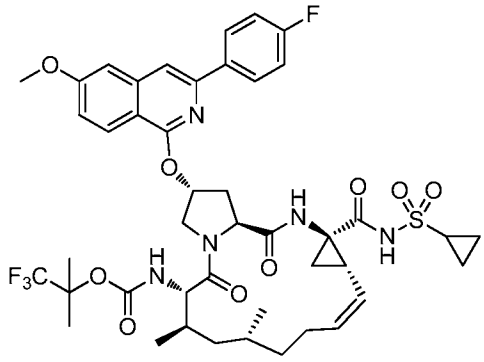
Compound 3041: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 848.5 (M^++1).

Compound 3042: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.22 (br. s., 1H), 8.94 (br. s., 1H), 8.29 - 8.21 (m, 2H), 8.06 (d, *J*=9.2 Hz, 1H), 7.92 (s, 1H), 7.41 - 7.31 (m, 3H), 7.22 (br. s., 1H), 7.10 (dd, *J*=9.2, 2.4 Hz, 1H), 5.97 (br. s., 1H), 5.60 - 5.46 (m, 1H), 5.15 - 5.00 (m, 1H), 4.71 - 4.57 (m, 1H), 4.51 - 4.39 (m, 1H), 4.00 - 3.89 (m, 4H), 3.80 - 3.71 (m, 1H), 2.91 (s, 1H), 2.79 - 2.64 (m, 2H), 2.44 - 2.23 (m, 2H), 2.00 - 0.67 (m, 28H); MS: MS *m/z* 848.5 (M^++1).

Preparation of Compound 3043 and Compound 3044



Compound 3043



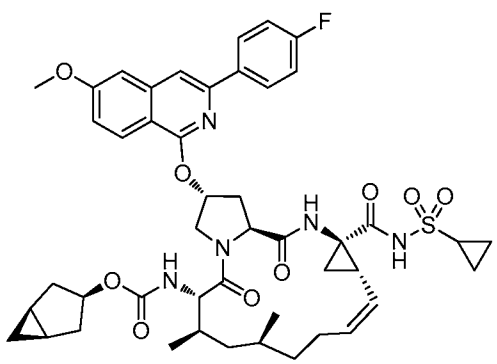
Compound 3044

Compounds 3043 and 3044 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

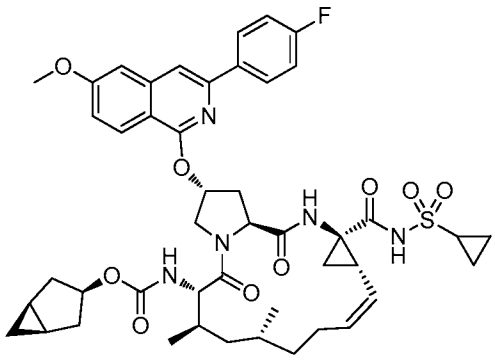
Compound 3043: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 902.4 (M^++1).

Compound 3044: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.98 (s, 1H), 8.28 - 8.21 (m, 2H), 8.03 (d, *J*=9.2 Hz, 1H), 7.93 (s, 1H), 7.86 (d, *J*=7.6 Hz, 1H), 7.41 - 7.34 (m, 3H), 7.13 (dd, *J*=8.9, 2.4 Hz, 1H), 5.99 (br. s., 1H), 5.59 - 5.48 (m, 1H), 5.07 (t, *J*=9.8 Hz, 1H), 4.57 (d, *J*=11.3 Hz, 1H), 4.50 (dd, *J*=10.1, 7.0 Hz, 1H), 4.01 - 3.89 (m, 4H), 3.74 (dd, *J*=10.7, 7.9 Hz, 1H), 2.99 - 2.88 (m, 1H), 2.77 - 2.64 (m, 2H), 2.43 - 2.25 (m, 2H), 1.98 - 1.80 (m, 2H), 1.73 (dd, *J*=12.7, 6.6 Hz, 1H), 1.65 - 1.52 (m, 2H), 1.50 - 0.84 (m, 19H), 0.76 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 902.4 (M^++1).

Preparation of Compound 3045 and Compound 3046



Compound 3045



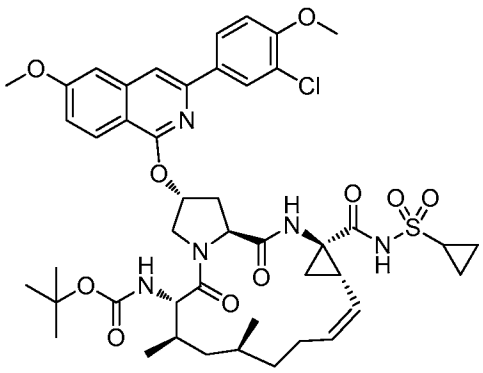
Compound 3046

Compounds 3045 and 3046 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

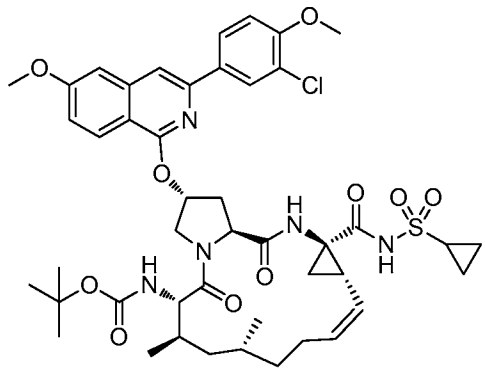
Compound 3045: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 872.5 (M^++1).

Compound 3046: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (br. s., 1H), 8.91 (br. s., 1H), 8.29 - 8.20 (m, 2H), 8.04 (d, *J*=8.9 Hz, 1H), 7.93 (s, 1H), 7.46 - 7.33 (m, 4H), 7.16 (dd, *J*=9.0, 2.6 Hz, 1H), 5.97 (br. s., 1H), 5.59 - 5.41 (m, 1H), 5.19 - 4.99 (m, 1H), 4.70 (t, *J*=6.7 Hz, 1H), 4.60 - 4.38 (m, 2H), 3.99 (d, *J*=7.9 Hz, 1H), 3.93 (s, 3H), 3.79 (t, *J*=9.6 Hz, 1H), 2.98 - 2.83 (m, 1H), 2.79 - 2.60 (m, 2H), 2.45 - 2.20 (m, 2H), 2.05 - 0.29 (m, 27H); MS: MS *m/z* 872.5 (M^++1).

Preparation of Compound 3047 and Compound 3048



Compound 3047



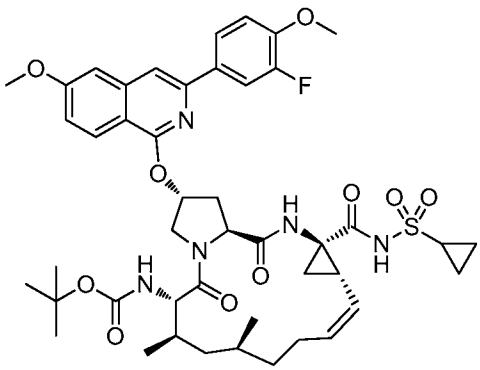
Compound 3048

Compounds 3047 and 3048 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

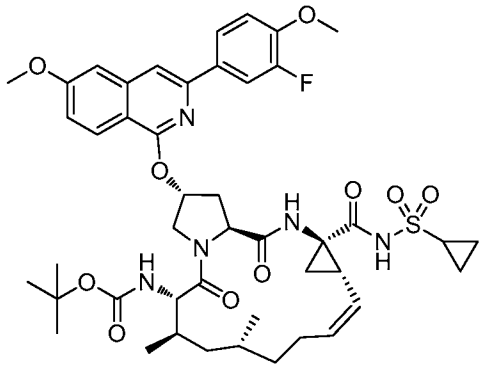
Compound 3047: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(3-chloro-4-methoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 894.6 (M^++1).

Compound 3048: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(3-chloro-4-methoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.24 (br. s., 1H), 8.78 (br. s., 1H), 8.22 (d, *J*=2.1 Hz, 1H), 8.16 (dd, *J*=8.5, 1.8 Hz, 1H), 8.05 (d, *J*=9.2 Hz, 1H), 7.93 (s, 1H), 7.37 - 7.30 (m, 2H), 7.19 (d, *J*=8.2 Hz, 1H), 7.07 (dd, *J*=9.0, 2.3 Hz, 1H), 5.96 (br. s., 1H), 5.55 - 5.40 (m, 1H), 5.34 - 5.06 (m, 1H), 4.58 (d, *J*=10.4 Hz, 1H), 4.43 (t, *J*=8.2 Hz, 1H), 4.01 - 3.89 (m, 7H), 3.81 - 3.72 (m, 1H), 2.89 - 2.80 (m, 1H), 2.72 - 2.57 (m, 2H), 2.43 - 2.23 (m, 2H), 1.99 - 0.63 (m, 28H); MS: MS *m/z* 894.5 (M^++1).

Preparation of Compound 3049 and Compound 3050



Compound 3049



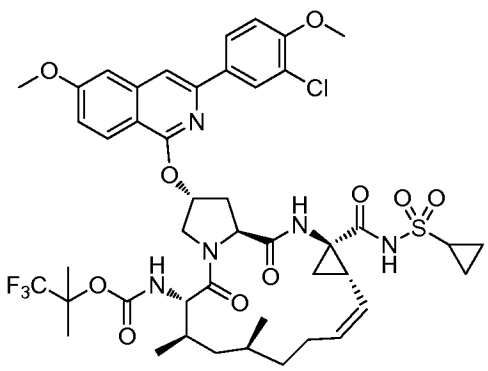
Compound 3050

Compounds 3049 and 3050 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

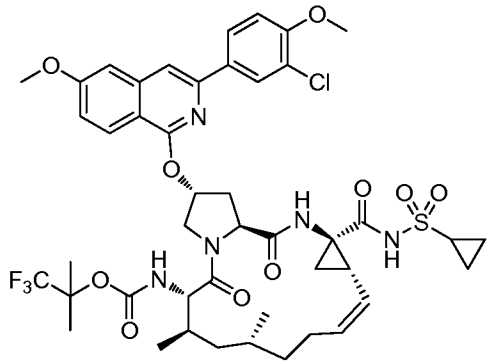
Compound 3049: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-methoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 878.5 (M^++1).

Compound 3050: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-methoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.23 (br. s., 1H), 8.89 (br. s., 1H), 8.08 - 7.98 (m, 3H), 7.90 (s, 1H), 7.38 - 7.29 (m, 2H), 7.18 (d, *J*=8.2 Hz, 1H), 7.08 (dd, *J*=8.9, 2.4 Hz, 1H), 5.96 (br. s., 1H), 5.56 - 5.40 (m, 1H), 5.30 - 5.05 (m, 1H), 4.63 - 4.53 (m, 1H), 4.43 (t, *J*=8.5 Hz, 1H), 4.02 - 3.89 (m, 7H), 3.76 (dd, *J*=10.5, 8.7 Hz, 1H), 2.88 - 2.80 (m, 1H), 2.72 - 2.60 (m, 2H), 2.44 - 2.23 (m, 2H), 2.00 - 0.62 (m, 28H); MS: MS *m/z* 878.6 (M^++1).

Preparation of Compound 3051 and Compound 3052



Compound 3051



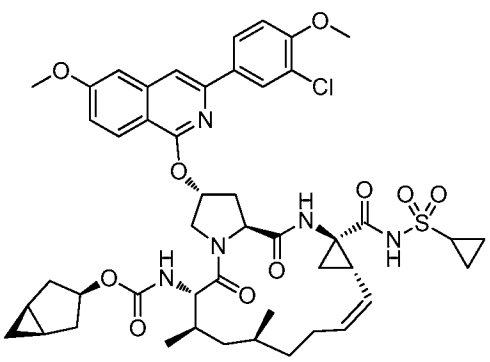
Compound 3052

Compounds 3051 and 3052 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

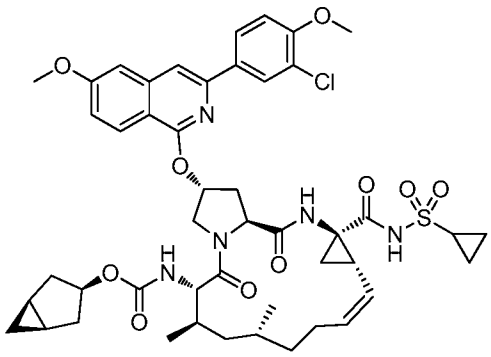
Compound 3051: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(3-chloro-4-methoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 948.6 (M^++1).

Compound 3052: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(3-chloro-4-methoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, METHANOL-d_4) δ 8.16 (d, *J*=2.1 Hz, 1H), 8.09 (dd, *J*=8.5, 2.1 Hz, 1H), 8.05 (d, *J*=9.2 Hz, 1H), 7.68 (s, 1H), 7.23 (d, *J*=2.4 Hz, 1H), 7.18 (d, *J*=8.9 Hz, 1H), 7.04 (dd, *J*=8.9, 2.4 Hz, 1H), 5.99 (br. s., 1H), 5.61 - 5.52 (m, 1H), 4.74 (d, *J*=11.6 Hz, 1H), 4.66 - 4.58 (m, 2H), 4.08 (dd, *J*=11.6, 3.4 Hz, 1H), 3.95 (d, *J*=8.9 Hz, 6H), 3.87 (d, *J*=10.7 Hz, 1H), 2.94 - 2.88 (m, 1H), 2.79 (dd, *J*=13.9, 7.2 Hz, 1H), 2.68 - 2.59 (m, 1H), 2.54 - 2.45 (m, 1H), 2.43 - 2.32 (m, 1H), 2.02 - 1.92 (m, 1H), 1.91 - 1.84 (m, 1H), 1.80 (dd, *J*=13.1, 5.2 Hz, 1H), 1.74 (dd, *J*=8.1, 5.3 Hz, 1H), 1.57 (dd, *J*=9.5, 5.2 Hz, 1H), 1.54 - 0.77 (m, 20H); MS: MS *m/z* 948.6 (M^++1).

Preparation of Compound 3053 and Compound 3054



Compound 3053



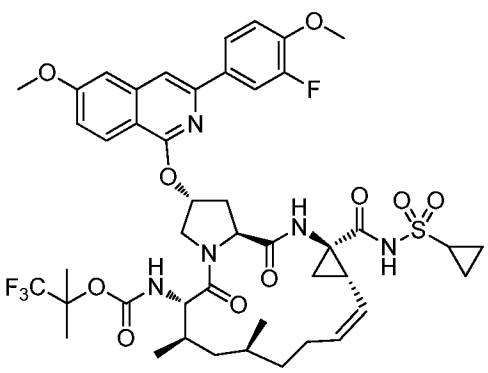
Compound 3054

Compounds 3053 and 3054 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

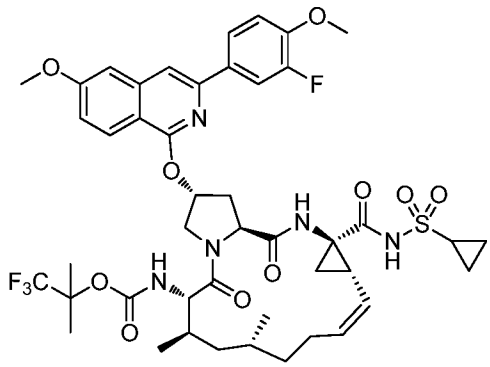
Compound 3053: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(3-chloro-4-methoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 918.5 (M^++1).

Compound 3054: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(3-chloro-4-methoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, METHANOL-d_4) δ 8.16 (s, 1H), 8.08 (dd, *J*=8.9, 2.1 Hz, 1H), 8.04 (d, *J*=8.9 Hz, 1H), 7.68 (s, 1H), 7.23 (d, *J*=2.1 Hz, 1H), 7.17 (d, *J*=8.5 Hz, 1H), 7.06 (dd, *J*=9.2, 2.4 Hz, 1H), 6.02 (br. s., 1H), 5.58 - 5.47 (m, 1H), 4.67 (t, *J*=6.7 Hz, 1H), 4.65 - 4.55 (m, 2H), 4.10 (dd, *J*=11.6, 3.4 Hz, 1H), 3.99 - 3.91 (m, 7H), 2.92 - 2.85 (m, 1H), 2.80 (dd, *J*=13.7, 7.0 Hz, 1H), 2.61 (br. s., 1H), 2.54 - 2.45 (m, 1H), 2.41 - 2.28 (m, 1H), 2.07 - 0.76 (m, 26H), 0.41 - 0.29 (m, 2H); MS: MS *m/z* 918.5 (M^++1).

Preparation of Compound 3055 and Compound 3056



Compound 3055



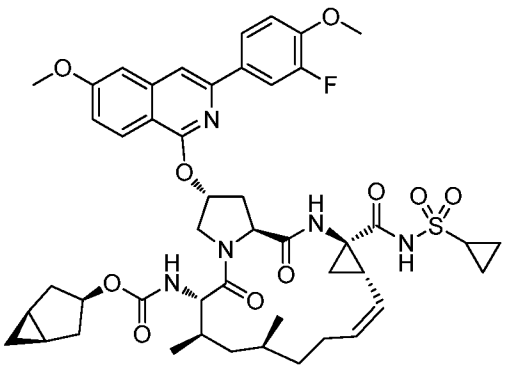
Compound 3056

Compounds 3055 and 3056 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

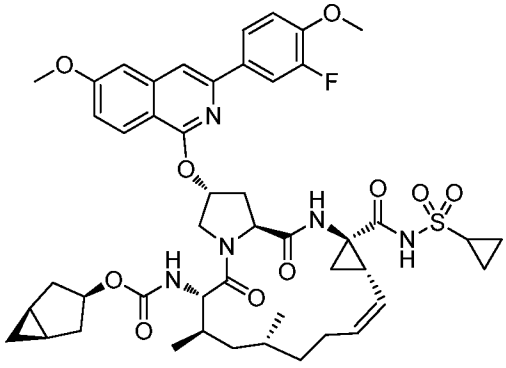
Compound 3055: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-methoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 932.5 (M^++1).

Compound 3056: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-methoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, METHANOL-d_4) δ 8.05 (d, *J*=9.2 Hz, 1H), 8.01 - 7.89 (m, 2H), 7.69 (s, 1H), 7.23 (d, *J*=2.4 Hz, 1H), 7.20 (t, *J*=8.7 Hz, 1H), 7.04 (dd, *J*=9.2, 2.4 Hz, 1H), 6.00 (br. s., 1H), 5.57 (td, *J*=9.9, 6.1 Hz, 1H), 4.74 (d, *J*=11.3 Hz, 1H), 4.67 - 4.58 (m, 2H), 4.09 (dd, *J*=11.6, 3.7 Hz, 1H), 3.95 (d, *J*=2.7 Hz, 6H), 3.87 (d, *J*=10.7 Hz, 1H), 2.95 - 2.88 (m, 1H), 2.79 (dd, *J*=13.7, 7.3 Hz, 1H), 2.70 - 2.60 (m, 1H), 2.49 (ddd, *J*=13.9, 10.1, 4.1 Hz, 1H), 2.44 - 2.32 (m, 1H), 2.01 - 1.92 (m, 1H), 1.91 - 1.84 (m, 1H), 1.80 (dd, *J*=13.1, 5.5 Hz, 1H), 1.74 (dd, *J*=8.4, 5.3 Hz, 1H), 1.60 - 0.92 (m, 20H), 0.83 (t, *J*=11.4 Hz, 1H); MS: MS *m/z* 932.5 (M^++1).

Preparation of Compound 3057 and Compound 3058



Compound 3057



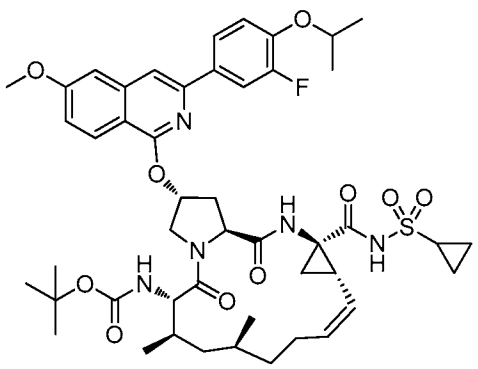
Compound 3058

Compounds 3057 and 3058 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

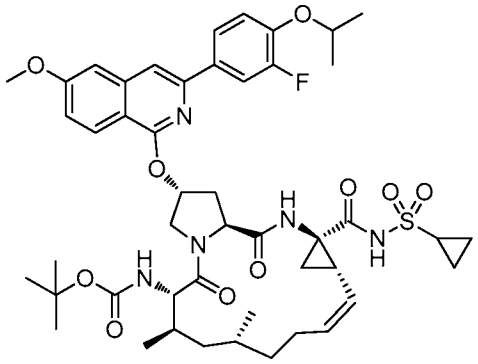
Compound 3057: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-methoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 902.6 (M^++1).

Compound 3058: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-methoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, METHANOL-d_4) δ 8.04 (d, *J*=8.9 Hz, 1H), 8.00 - 7.88 (m, 2H), 7.69 (s, 1H), 7.23 (d, *J*=2.1 Hz, 1H), 7.19 (t, *J*=8.7 Hz, 1H), 7.06 (dd, *J*=9.2, 2.4 Hz, 1H), 6.01 (br. s., 1H), 5.54 - 5.45 (m, 1H), 4.67 (t, *J*=6.9 Hz, 1H), 4.64 - 4.55 (m, 2H), 4.12 (dd, *J*=11.4, 3.5 Hz, 1H), 4.00 - 3.92 (m, 7H), 2.91 - 2.76 (m, 2H), 2.60 - 2.47 (m, 2H), 2.40 - 2.27 (m, 1H), 2.06 - 0.74 (m, 26H), 0.41 - 0.29 (m, 2H); MS: MS *m/z* 902.6 (M^++1).

Preparation of Compound 3059 and Compound 3060



Compound 3059



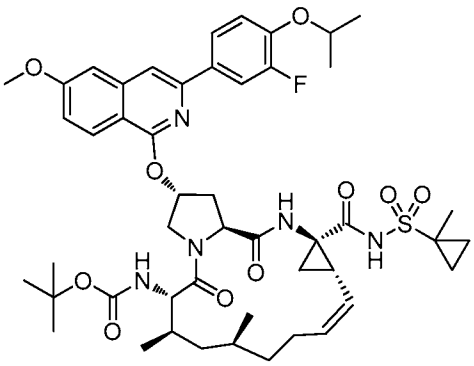
Compound 3060

Compounds 3059 and 3060 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

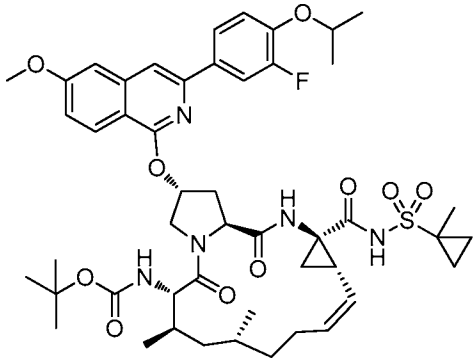
Compound 3059: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 906.8 (M^++1).

Compound 3060: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.22 (br. s., 1H), 8.94 (br. s., 1H), 8.08 - 7.95 (m, 3H), 7.90 (s, 1H), 7.38 - 7.29 (m, 2H), 7.21 (d, *J*=7.0 Hz, 1H), 7.08 (dd, *J*=9.0, 2.3 Hz, 1H), 5.98 (br. s., 1H), 5.61 - 5.46 (m, 1H), 5.13 - 5.00 (m, 1H), 4.75 (spt, *J*=6.0 Hz, 1H), 4.65 - 4.54 (m, 1H), 4.45 (t, *J*=8.5 Hz, 1H), 4.01 - 3.88 (m, 4H), 3.80 - 3.71 (m, 1H), 2.91 (s, 1H), 2.79 - 2.62 (m, 2H), 2.43 - 2.24 (m, 2H), 2.02 - 0.63 (m, 34H); MS: MS *m/z* 906.8 (M^++1).

Preparation of Compound 3061 and Compound 3062



Compound 3061



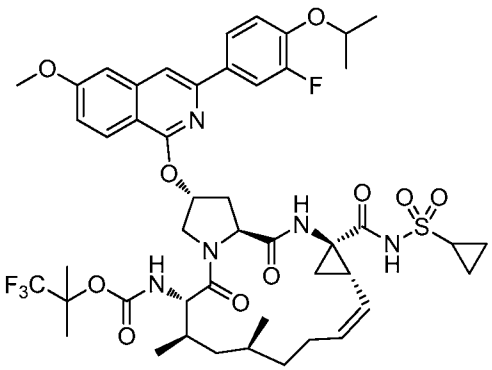
Compound 3062

Compounds 3061 and 3062 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

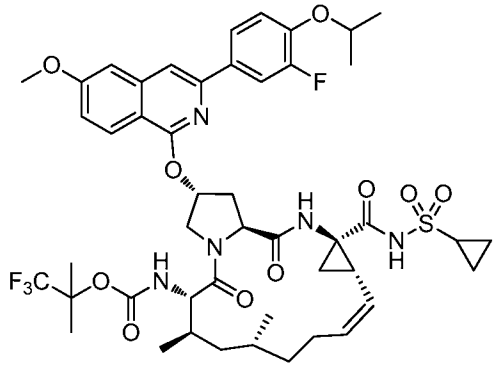
Compound 3061: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 920.7 (M^++1).

Compound 3062: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.07 (br. s., 1H), 9.08 (br. s., 1H), 8.08 - 7.94 (m, 4H), 7.90 (s, 1H), 7.37 - 7.30 (m, 2H), 7.21 (d, *J*=7.9 Hz, 1H), 7.08 (dd, *J*=9.0, 2.3 Hz, 1H), 6.00 (br. s., 1H), 5.59 - 5.48 (m, 1H), 4.99 (t, *J*=9.3 Hz, 1H), 4.75 (spt, *J*=6.1 Hz, 1H), 4.61 (d, *J*=11.0 Hz, 1H), 4.49 (t, *J*=8.1 Hz, 1H), 4.03 - 3.95 (m, 1H), 3.92 (s, 3H), 3.80 - 3.71 (m, 1H), 2.78 - 2.62 (m, 2H), 2.42 - 2.28 (m, 2H), 1.99 - 0.84 (m, 35H), 0.76 (t, *J*=12.7 Hz, 1H); MS: MS *m/z* 920.8 (M^++1).

Preparation of Compound 3063 and Compound 3064



Compound 3063



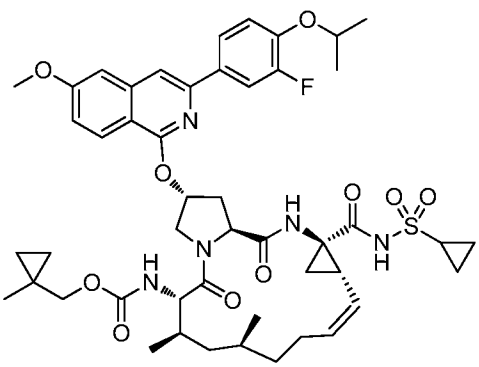
Compound 3064

Compounds 3063 and 3064 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

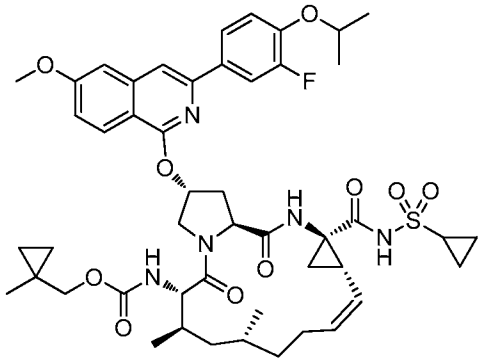
Compound 3063: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 960.8 (M^++1).

Compound 3064: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.22 (s, 1H), 8.98 (br. s., 1H), 8.06 - 7.95 (m, 3H), 7.91 (s, 1H), 7.85 (d, *J*=7.6 Hz, 1H), 7.38 - 7.29 (m, 2H), 7.12 (dd, *J*=9.2, 2.4 Hz, 1H), 6.00 (br. s., 1H), 5.59 - 5.48 (m, 1H), 5.07 (t, *J*=9.3 Hz, 1H), 4.75 (spt, *J*=6.0 Hz, 1H), 4.62 - 4.45 (m, 2H), 4.01 - 3.89 (m, 4H), 3.74 (dd, *J*=10.7, 7.9 Hz, 1H), 2.98 - 2.88 (m, 1H), 2.74 - 2.62 (m, 2H), 2.42 - 2.24 (m, 2H), 1.99 - 0.70 (m, 31H); MS: MS *m/z* 960.8 (M^++1).

Preparation of Compound 3065 and Compound 3066



Compound 3065



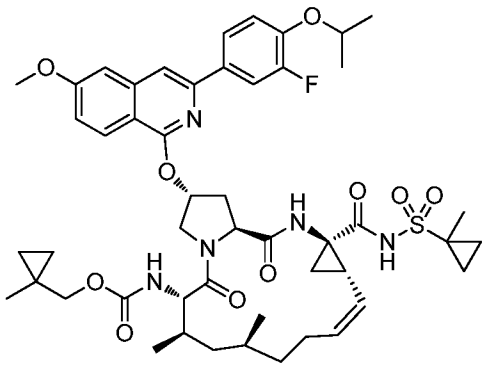
Compound 3066

Compounds 3065 and 3066 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

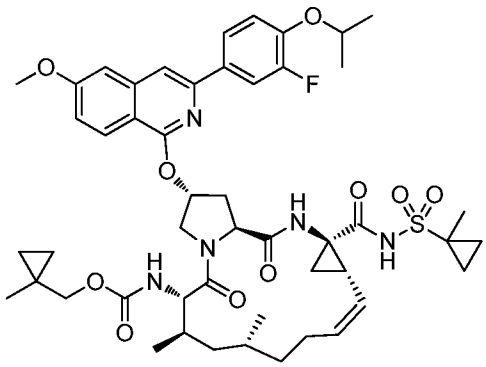
Compound 3065: (1-methylcyclopropyl)methyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 918.8 (M^++1).

Compound 3066: (1-methylcyclopropyl)methyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.22 (br. s., 1H), 8.93 (br. s., 1H), 8.06 - 7.95 (m, 3H), 7.90 (s, 1H), 7.52 (br. s., 1H), 7.38 - 7.29 (m, 2H), 7.11 (dd, *J*=9.2, 2.4 Hz, 1H), 5.99 (br. s., 1H), 5.63 - 5.42 (m, 1H), 5.19 - 5.00 (m, 1H), 4.75 (spt, *J*=6.1 Hz, 2H), 4.61 - 4.38 (m, 2H), 4.03 - 3.96 (m, 1H), 3.93 (s, 3H), 3.78 (t, *J*=9.6 Hz, 1H), 3.52 - 3.41 (m, 2H), 2.91 (s, 1H), 2.77 - 2.61 (m, 2H), 2.45 - 2.22 (m, 2H), 2.01 - 0.65 (m, 27H), 0.35 - 0.18 (m, 4H); MS: MS *m/z* 918.9 (M^++1).

Preparation of Compound 3067 and Compound 3068



Compound 3067



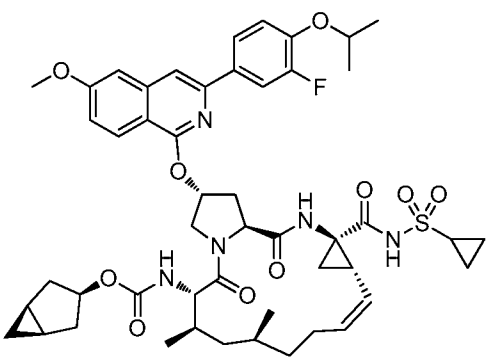
Compound 3068

Compounds 3067 and 3068 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

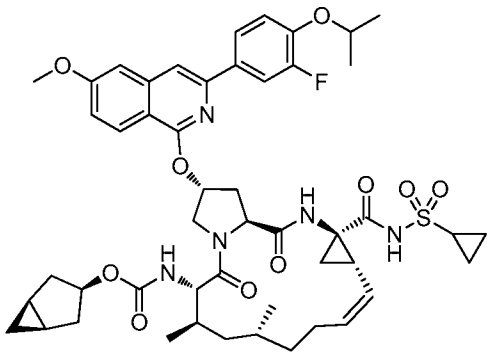
Compound 3067: (1-methylcyclopropyl)methyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 932.8 (M^++1).

Compound 3068: (1-methylcyclopropyl)methyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.07 (br. s., 1H), 9.06 (br. s., 1H), 8.05 - 7.93 (m, 3H), 7.90 (s, 1H), 7.53 (d, *J*=7.9 Hz, 1H), 7.37 - 7.30 (m, 2H), 7.11 (dd, *J*=9.2, 2.4 Hz, 1H), 6.02 (br. s., 1H), 5.61 - 5.48 (m, 1H), 5.07 - 4.95 (m, 1H), 4.75 (spt, *J*=6.1 Hz, 1H), 4.61 - 4.45 (m, 2H), 4.01 (dd, *J*=11.1, 3.2 Hz, 1H), 3.96 - 3.90 (m, 3H), 3.78 (dd, *J*=10.5, 8.7 Hz, 1H), 3.50 - 3.39 (m, 2H), 2.78 - 2.63 (m, 2H), 2.43 - 2.27 (m, 2H), 2.00 - 0.67 (m, 31H), 0.34 - 0.17 (m, 4H); MS: MS *m/z* 932.9 (M^++1).

Preparation of Compound 3069 and Compound 3070



Compound 3069



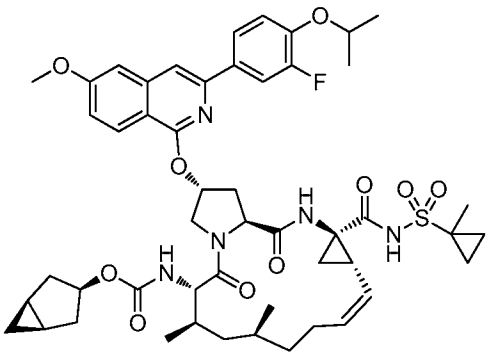
Compound 3070

Compounds 3069 and 3070 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

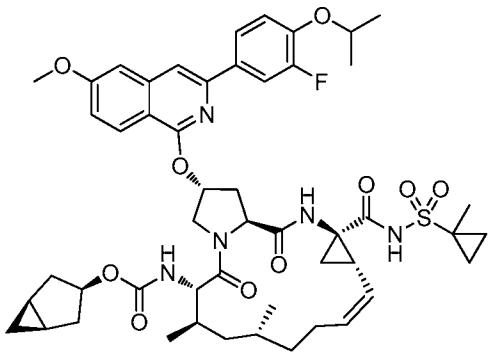
Compound 3069: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 930.8 (M^++1).

Compound 3070: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.22 (br. s., 1H), 8.90 (br. s., 1H), 8.06 - 7.95 (m, 3H), 7.91 (s, 1H), 7.42 (d, *J*=7.6 Hz, 1H), 7.38 - 7.29 (m, 2H), 7.14 (dd, *J*=9.0, 2.3 Hz, 1H), 5.99 (br. s., 1H), 5.60 - 5.44 (m, 1H), 5.17 - 5.02 (m, 1H), 4.82 - 4.66 (m, 2H), 4.57 - 4.40 (m, 2H), 4.04 - 3.96 (m, 1H), 3.93 (s, 3H), 3.83 - 3.73 (m, 1H), 2.97 - 2.87 (m, 1H), 2.79 - 2.60 (m, 2H), 2.44 - 2.20 (m, 2H), 2.04 - 0.66 (m, 31H), 0.45 - 0.32 (m, 2H); MS: MS *m/z* 930.7 (M^++1).

Preparation of Compound 3071 and Compound 3072



Compound 3071



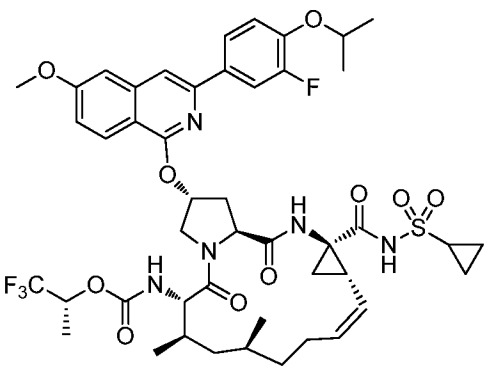
Compound 3072

Compounds 3071 and 3072 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

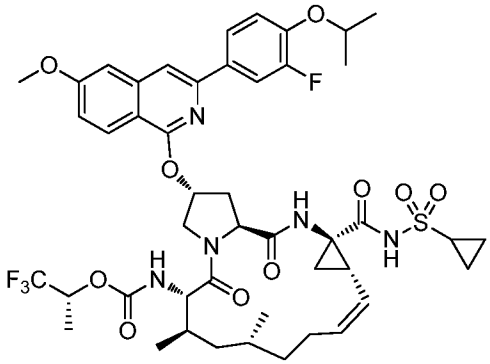
Compound 3071: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 944.8 (M^++1).

Compound 3072: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.07 (br. s., 1H), 9.04 (br. s., 1H), 8.04 - 7.94 (m, 3H), 7.91 (s, 1H), 7.43 (d, *J*=8.2 Hz, 1H), 7.37 - 7.28 (m, 2H), 7.14 (dd, *J*=8.9, 2.4 Hz, 1H), 6.02 (br. s., 1H), 5.59 - 5.49 (m, 1H), 5.06 - 4.94 (m, 1H), 4.75 (spt, *J*=6.0 Hz, 1H), 4.68 (t, *J*=6.6 Hz, 1H), 4.55 - 4.46 (m, 2H), 4.01 (dd, *J*=11.1, 3.5 Hz, 1H), 3.93 (s, 3H), 3.83 - 3.75 (m, 1H), 2.79 - 2.63 (m, 2H), 2.42 - 2.25 (m, 2H), 2.02 - 1.76 (m, 4H), 1.72 - 0.71 (m, 30H), 0.44 - 0.32 (m, 2H); MS: MS *m/z* 944.7 (M^++1).

Preparation of Compound 3073 and Compound 3074



Compound 3073



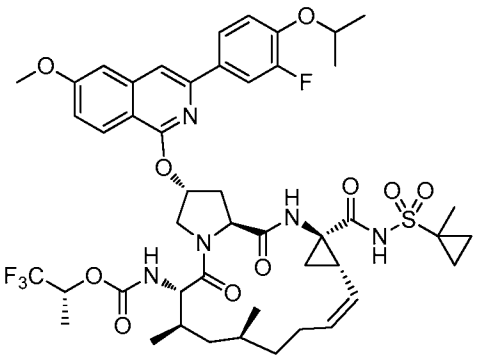
Compound 3074

Compounds 3073 and 3074 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

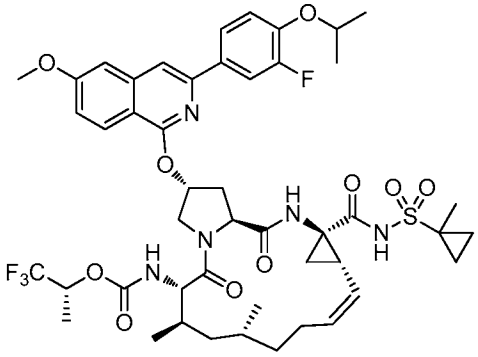
Compound 3073: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 946.7 (M^++1).

Compound 3074: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (br. s., 1H), 8.93 (br. s., 1H), 8.10 (d, *J*=7.3 Hz, 1H), 8.05 - 7.95 (m, 3H), 7.91 (s, 1H), 7.37 - 7.30 (m, 2H), 7.06 (dd, *J*=8.9, 2.4 Hz, 1H), 5.99 (br. s., 1H), 5.60 - 5.45 (m, 1H), 5.18 - 5.01 (m, 1H), 4.82 (quin, *J*=6.9 Hz, 1H), 4.75 (spt, *J*=6.0 Hz, 1H), 4.60 - 4.50 (m, 1H), 4.46 (t, *J*=8.2 Hz, 1H), 3.99 (d, *J*=7.9 Hz, 1H), 3.92 (s, 3H), 3.81 (dd, *J*=10.7, 8.2 Hz, 1H), 2.91 (s, 1H), 2.78 - 2.59 (m, 2H), 2.44 - 2.23 (m, 2H), 2.01 - 0.66 (m, 28H); MS: MS *m/z* 946.7 (M^++1).

Preparation of Compound 3075 and Compound 3076



Compound 3075



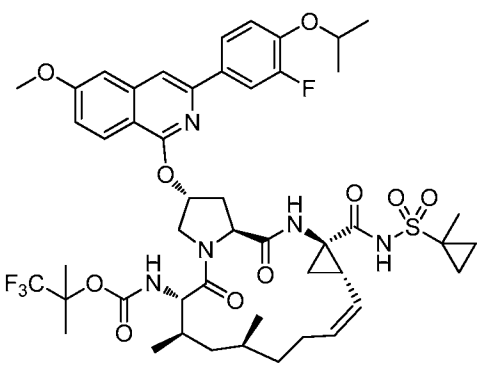
Compound 3076

Compounds 3075 and 3076 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

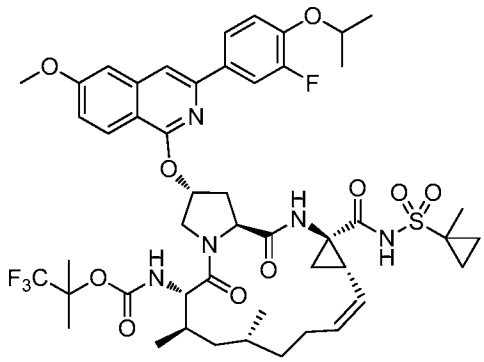
Compound 3075: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 960.7 (M^++1).

Compound 3076: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.07 (br. s., 1H), 8.10 (d, *J*=7.3 Hz, 1H), 8.04 - 7.94 (m, 3H), 7.91 (s, 1H), 7.39 - 7.29 (m, 2H), 7.06 (dd, *J*=9.0, 2.3 Hz, 1H), 6.01 (br. s., 1H), 5.60 - 5.47 (m, 1H), 5.06 - 4.96 (m, 1H), 4.86 - 4.69 (m, 2H), 4.64 - 4.44 (m, 2H), 4.01 (dd, *J*=11.0, 3.4 Hz, 1H), 3.92 (s, 3H), 3.80 (dd, *J*=10.7, 8.2 Hz, 1H), 2.77 - 2.62 (m, 2H), 2.44 - 2.27 (m, 2H), 1.98 - 1.83 (m, 2H), 1.80 - 0.67 (m, 29H); MS: MS *m/z* 960.7 (M^++1).

Preparation of Compound 3077 and Compound 3078



Compound 3077



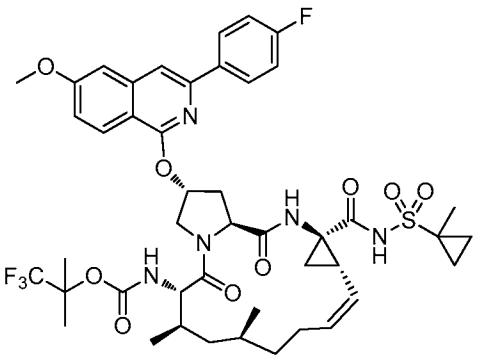
Compound 3078

Compounds 3077 and 3078 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

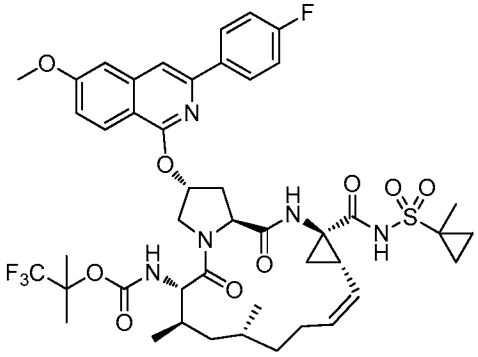
Compound 3077: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 974.8 (M^++1).

Compound 3078: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(3-fluoro-4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.07 (br. s., 1H), 8.10 (d, *J*=7.3 Hz, 1H), 8.04 - 7.94 (m, 3H), 7.91 (s, 1H), 7.39 - 7.29 (m, 2H), 7.06 (dd, *J*=9.0, 2.3 Hz, 1H), 6.01 (br. s., 1H), 5.60 - 5.47 (m, 1H), 5.06 - 4.96 (m, 1H), 4.86 - 4.69 (m, 2H), 4.64 - 4.44 (m, 2H), 4.01 (dd, *J*=11.0, 3.4 Hz, 1H), 3.92 (s, 3H), 3.80 (dd, *J*=10.7, 8.2 Hz, 1H), 2.77 - 2.62 (m, 2H), 2.44 - 2.27 (m, 2H), 1.98 - 1.83 (m, 2H), 1.80 - 0.67 (m, 29H); MS: MS *m/z* 974.8 (M^++1).

Preparation of Compound 3079 and Compound 3080



Compound 3079



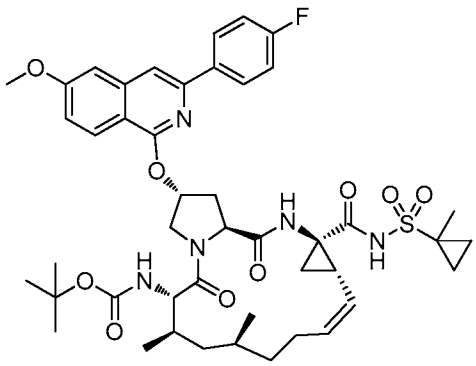
Compound 3080

Compounds 3079 and 3080 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

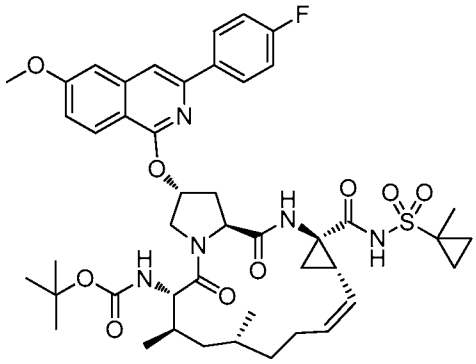
Compound 3079: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 916.7 (M^++1).

Compound 3080: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (br. s., 1H), 9.11 (br. s., 1H), 8.24 (dd, *J*=8.9, 5.5 Hz, 2H), 8.03 (d, *J*=9.2 Hz, 1H), 7.93 (s, 1H), 7.85 (d, *J*=7.6 Hz, 1H), 7.41 - 7.31 (m, 3H), 7.14 (dd, *J*=9.2, 2.4 Hz, 1H), 6.00 (br. s., 1H), 5.61 - 5.47 (m, 1H), 5.08 - 4.94 (m, 1H), 4.64 - 4.47 (m, 2H), 3.98 (dd, *J*=11.4, 3.2 Hz, 1H), 3.93 (s, 3H), 3.74 (dd, *J*=10.7, 8.2 Hz, 1H), 2.79 - 2.62 (m, 2H), 2.43 - 2.26 (m, 2H), 1.96 - 0.70 (m, 28H); MS: MS *m/z* 916.7 (M^++1).

Preparation of Compound 3081 and Compound 3082



Compound 3081



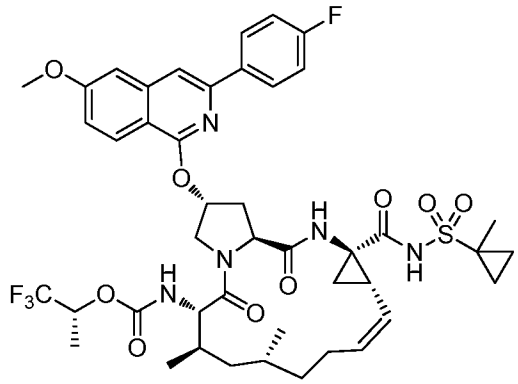
Compound 3082

Compounds 3081 and 3082 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 3081: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 862.7.7 (M^++1).

Compound 3082: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.07 (br. s., 1H), 9.08 (br. s., 1H), 8.23 (dd, *J*=8.9, 5.8 Hz, 2H), 8.06 (d, *J*=9.2 Hz, 1H), 7.92 (s, 1H), 7.40 - 7.33 (m, 3H), 7.21 (d, *J*=7.9 Hz, 1H), 7.10 (dd, *J*=9.2, 2.4 Hz, 1H), 5.99 (br. s., 1H), 5.60 - 5.48 (m, 1H), 5.05 - 4.93 (m, 1H), 4.68 - 4.60 (m, 1H), 4.53 - 4.46 (m, 1H), 3.98 (dd, *J*=11.0, 3.1 Hz, 1H), 3.93 (s, 3H), 3.75 (dd, *J*=10.8, 8.4 Hz, 1H), 2.79 - 2.64 (m, 2H), 2.43 - 2.26 (m, 2H), 1.99 - 0.69 (m, 31H); MS: MS *m/z* 862.7 (M^++1).

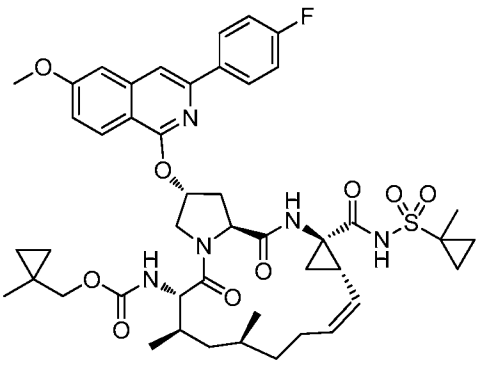
Preparation of Compound 3083



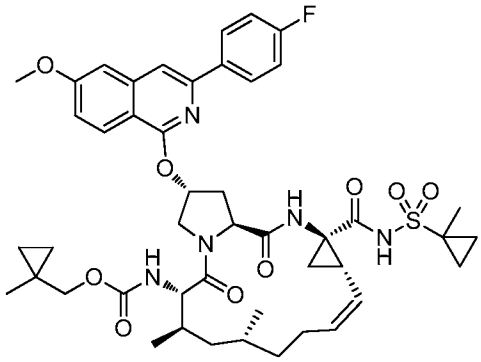
Compound 3083

Compound 3083 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117: Compound 3083: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.08 (br. s., 1H), 8.27 - 8.21 (m, 2H), 8.11 (d, *J*=7.9 Hz, 1H), 8.00 (d, *J*=9.2 Hz, 1H), 7.93 (s, 1H), 7.41 - 7.33 (m, 3H), 7.07 (dd, *J*=9.2, 2.4 Hz, 1H), 6.01 (br. s., 1H), 5.59 - 5.48 (m, 1H), 5.00 (t, *J*=9.2 Hz, 1H), 4.80 (dt, *J*=13.4, 6.7 Hz, 1H), 4.57 (d, *J*=11.3 Hz, 1H), 4.54 - 4.46 (m, 1H), 4.00 (dd, *J*=11.3, 3.4 Hz, 1H), 3.92 (s, 3H), 3.81 (dd, *J*=10.7, 8.2 Hz, 1H), 2.79 - 2.63 (m, 2H), 2.43 - 2.27 (m, 2H), 2.00 - 1.84 (m, 2H), 1.76 - 0.72 (m, 23H); MS: MS *m/z* 902.7 (M^++1).

Preparation of Compound 3084 and Compound 3085



Compound 3084



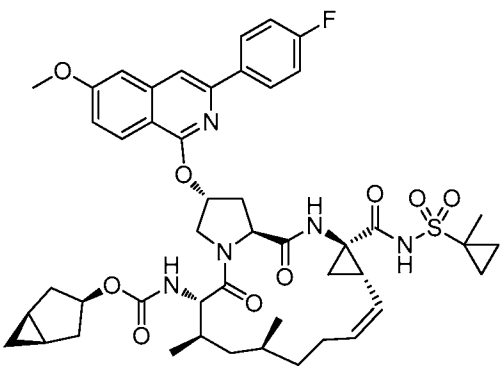
Compound 3085

Compounds 3084 and 3085 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

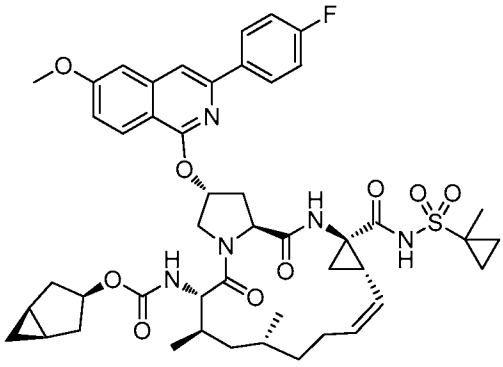
Compound 3084: (1-methylcyclopropyl)methyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 874.8 (M^++1).

Compound 3085: (1-methylcyclopropyl)methyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.07 (br. s., 1H), 9.06 (br. s., 1H), 8.23 (dd, *J*=8.5, 5.5 Hz, 2H), 8.04 (d, *J*=8.9 Hz, 1H), 7.93 (s, 1H), 7.54 (d, *J*=8.2 Hz, 1H), 7.41 - 7.32 (m, *J*=17.7 Hz, 3H), 7.13 (dd, *J*=9.0, 2.3 Hz, 1H), 6.01 (br. s., 1H), 5.58 - 5.48 (m, 1H), 5.06 - 4.94 (m, 1H), 4.58 (d, *J*=11.3 Hz, 1H), 4.51 (t, *J*=8.1 Hz, 1H), 4.00 (dd, *J*=11.4, 3.2 Hz, 1H), 3.93 (s, 3H), 3.78 (dd, *J*=10.2, 8.7 Hz, 1H), 3.50 - 3.40 (m, 2H), 2.79 - 2.63 (m, 2H), 2.43 - 2.27 (m, 2H), 2.00 - 1.81 (m, 2H), 1.77 - 0.66 (m, 23H), 0.37 - 0.16 (m, 4H); MS: MS *m/z* 874.8 (M^++1).

Preparation of Compound 3086 and Compound 3087



Compound 3086



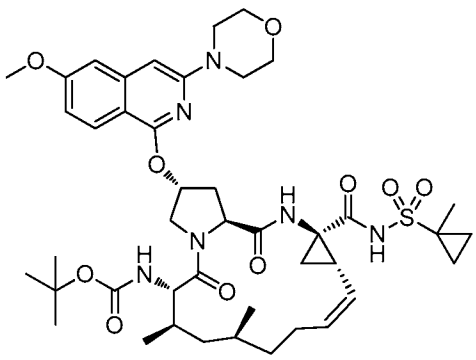
Compound 3087

Compounds 3086 and 3087 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

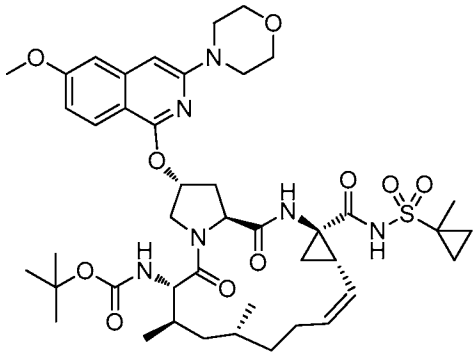
Compound 3086: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 886.7 (M^++1).

Compound 3087: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(4-fluorophenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.07 (br. s., 1H), 9.04 (br. s., 1H), 8.29 - 8.19 (m, 2H), 8.03 (d, *J*=9.2 Hz, 1H), 7.93 (s, 1H), 7.43 (d, *J*=8.2 Hz, 1H), 7.40 - 7.33 (m, 3H), 7.16 (dd, *J*=9.0, 2.3 Hz, 1H), 6.00 (br. s., 1H), 5.59 - 5.46 (m, 1H), 5.08 - 4.94 (m, 1H), 4.69 (t, *J*=6.6 Hz, 1H), 4.58 - 4.44 (m, 2H), 4.00 (dd, *J*=11.4, 3.5 Hz, 1H), 3.96 - 3.91 (m, 3H), 3.79 (t, *J*=9.8 Hz, 1H), 2.79 - 2.64 (m, 2H), 2.42 - 2.25 (m, 2H), 2.03 - 1.77 (m, 4H), 1.75 - 0.69 (m, 24H), 0.43 - 0.32 (m, 2H); MS: MS *m/z* 886.8 (M^++1).

Preparation of Compound 3088 and Compound **3089**



Compound 3088



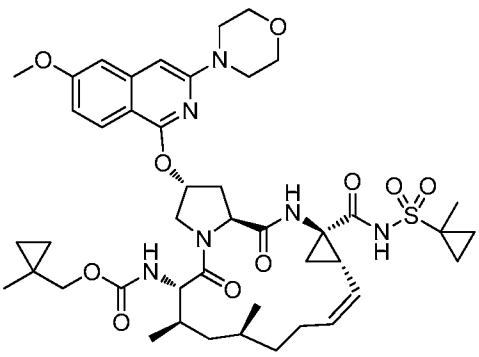
Compound 3089

Compounds 3088 and 3089 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

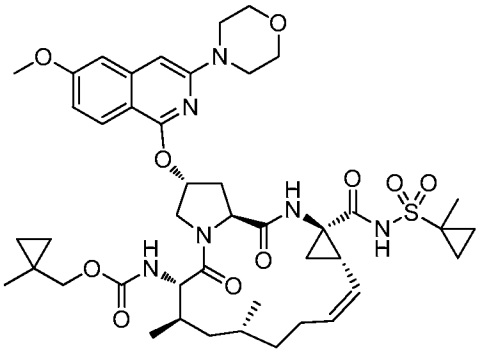
Compound 3088: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 853.8 (M^++1).

Compound 3089: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.07 (br. s., 1H), 9.06 (br. s., 1H), 7.84 (d, *J*=9.2 Hz, 1H), 7.22 (d, *J*=8.2 Hz, 1H), 7.00 (d, *J*=2.1 Hz, 1H), 6.72 (dd, *J*=9.0, 2.3 Hz, 1H), 6.45 (s, 1H), 5.76 (br. s., 1H), 5.61 - 5.47 (m, 1H), 5.04 - 4.91 (m, 1H), 4.52 (d, *J*=11.6 Hz, 1H), 4.43 (t, *J*=8.4 Hz, 1H), 3.95 - 3.89 (m, 1H), 3.84 (s, 3H), 3.80 - 3.72 (m, 5H), 3.51 - 3.39 (m, 4H), 2.71 (br. s., 1H), 2.63 - 2.54 (m, 1H), 2.40 - 2.22 (m, 2H), 1.97 - 1.79 (m, 2H), 1.76 - 0.83 (m, 28H), 0.74 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 853.8 (M^++1).

Preparation of Compound 3090 and Compound 3091



Compound 3090



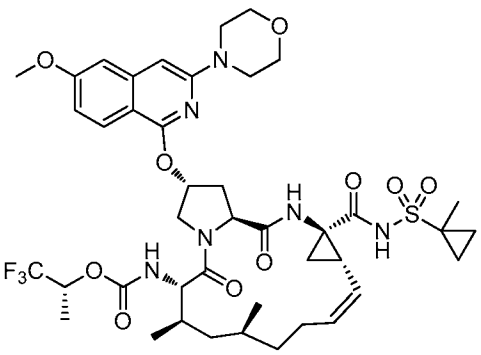
Compound 3091

Compounds 3090 and 3091 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

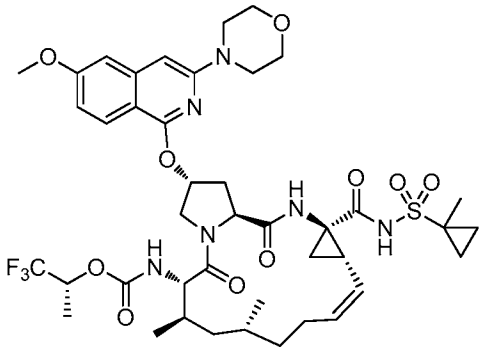
Compound 3090: (1-methylcyclopropyl)methyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 865.8 (M^++1).

Compound 3091: (1-methylcyclopropyl)methyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.04 (br. s., 1H), 7.81 (d, *J*=8.9 Hz, 1H), 7.54 (d, *J*=7.0 Hz, 1H), 7.01 (s, 1H), 6.79 - 6.73 (m, 1H), 6.46 (s, 1H), 5.76 (br. s., 1H), 5.57 - 5.45 (m, 1H), 5.12 - 4.94 (m, 1H), 4.42 (br. s., 1H), 3.95 (dd, *J*=11.4, 3.5 Hz, 1H), 3.85 (s, 3H), 3.77 (t, *J*=4.7 Hz, 5H), 3.50 - 3.40 (m, 4H), 2.61 - 2.54 (m, 2H), 2.36 - 2.25 (m, 2H), 1.98 - 0.65 (m, 31H), 0.40 - 0.19 (m, 4H); MS: MS *m/z* 865.8 (M^++1).

Preparation of Compound 3092 and Compound 3093



Compound 3092



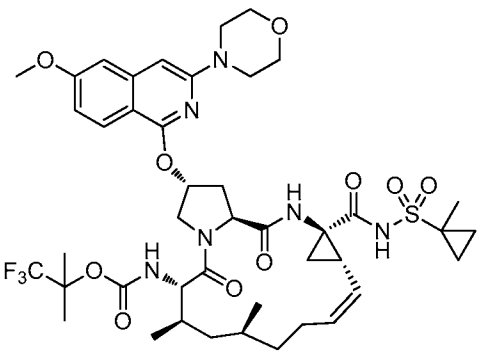
Compound 3093

Compounds 3092 and 3093 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

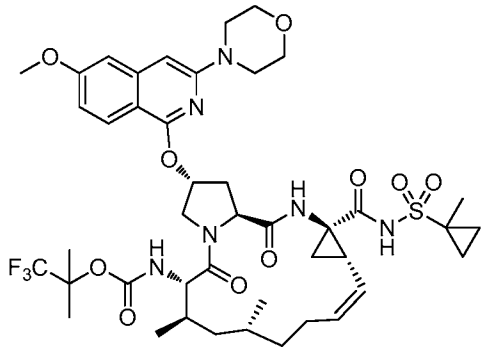
Compound 3092: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 893.6 (M^++1).

Compound 3093: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.06 (br. s., 1H), 8.12 (d, *J*=8.2 Hz, 1H), 7.78 (d, *J*=9.2 Hz, 1H), 7.01 (d, *J*=2.4 Hz, 1H), 6.70 (dd, *J*=9.0, 2.3 Hz, 1H), 6.46 (s, 1H), 5.77 (br. s., 1H), 5.59 - 5.47 (m, 1H), 5.03 - 4.92 (m, 2H), 4.51 - 4.39 (m, 2H), 3.95 (dd, *J*=11.4, 3.5 Hz, 1H), 3.87 - 3.80 (m, 4H), 3.79 - 3.75 (m, 4H), 3.50 - 3.39 (m, 4H), 2.72 - 2.56 (m, 2H), 2.41 - 2.22 (m, 2H), 1.98 - 1.82 (m, 2H), 1.75 - 1.66 (m, 1H), 1.63 - 1.56 (m, 1H), 1.55 - 0.70 (m, 21H); MS: MS *m/z* 893.7 (M^++1).

Preparation of Compound 3094 and Compound 3095



Compound 3094



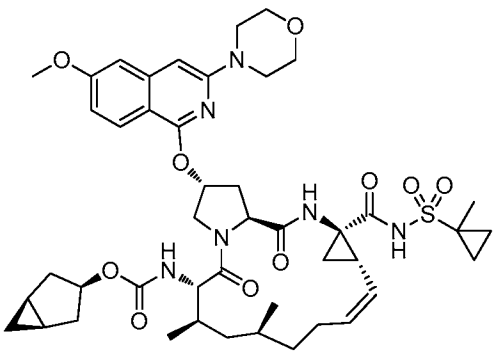
Compound 3095

Compounds 3094 and 3095 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

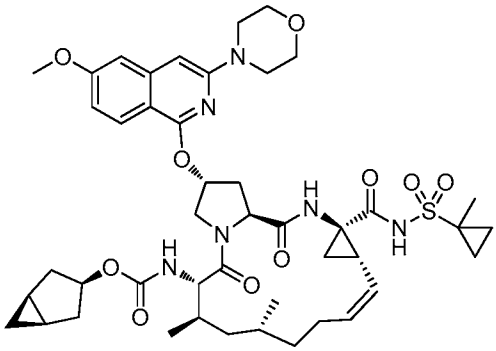
Compound 3094: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 907.7 (M^++1).

Compound 3095: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.08 (br. s., 1H), 7.86 (d, *J*=8.2 Hz, 1H), 7.81 (d, *J*=9.2 Hz, 1H), 7.01 (d, *J*=2.4 Hz, 1H), 6.76 (dd, *J*=9.2, 2.4 Hz, 1H), 6.46 (s, 1H), 5.76 (br. s., 1H), 5.57 - 5.45 (m, 1H), 5.15 - 4.90 (m, 1H), 4.53 - 4.39 (m, 2H), 3.97 - 3.89 (m, 1H), 3.84 (s, 3H), 3.80 - 3.74 (m, 5H), 3.51 - 3.39 (m, 4H), 2.69 - 2.55 (m, 2H), 2.42 - 2.23 (m, 2H), 1.97 - 1.81 (m, 2H), 1.77 - 0.68 (m, 26H); MS: MS *m/z* 907.7 (M^++1).

Preparation of Compound 3096 and Compound 3097



Compound 3096



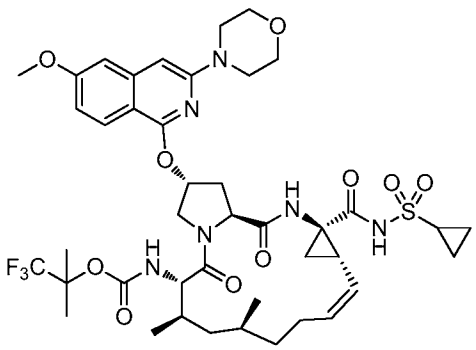
Compound 3097

Compounds 3096 and 3097 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

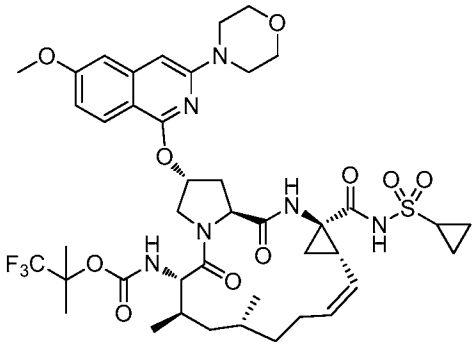
Compound 3096: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 877.8 (M^++1).

Compound 3097: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.00 (br. s., 1H), 7.81 (d, *J*=8.9 Hz, 1H), 7.43 (d, *J*=8.5 Hz, 1H), 7.02 (d, *J*=2.1 Hz, 1H), 6.78 (dd, *J*=9.0, 2.3 Hz, 1H), 6.47 (s, 1H), 5.76 (br. s., 1H), 5.58 - 5.45 (m, 1H), 5.13 - 4.96 (m, 1H), 4.81 (t, *J*=6.7 Hz, 1H), 4.48 - 4.36 (m, 2H), 3.95 (dd, *J*=11.0, 3.4 Hz, 1H), 3.85 (s, 3H), 3.83 - 3.75 (m, 5H), 3.50 - 3.41 (m, 4H), 2.63 - 2.53 (m, 2H), 2.36 - 2.22 (m, 2H), 2.08 - 1.79 (m, 4H), 1.72 - 1.09 (m, 15H), 0.99 - 0.67 (m, 9H), 0.46 - 0.33 (m, 2H); MS: MS *m/z* 877.7 (M^++1).

Preparation of Compound 3098 and Compound 3099



Compound 3098



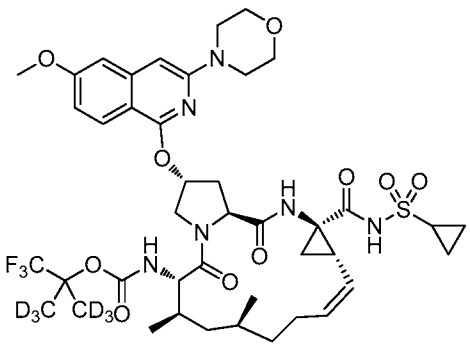
Compound 3099

Compounds 3098 and 3099 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

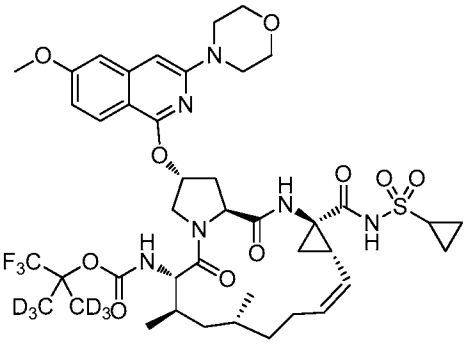
Compound 3098: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 893.8 (M^++1).

Compound 3099: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.20 (br. s., 1H), 8.96 (br. s., 1H), 7.86 (d, *J*=7.9 Hz, 1H), 7.81 (d, *J*=9.2 Hz, 1H), 7.01 (d, *J*=2.1 Hz, 1H), 6.75 (dd, *J*=9.0, 2.3 Hz, 1H), 6.46 (s, 1H), 5.75 (br. s., 1H), 5.58 - 5.46 (m, 1H), 5.13 - 4.99 (m, 1H), 4.50 - 4.40 (m, 2H), 3.93 - 3.88 (m, 1H), 3.84 (s, 3H), 3.80 - 3.73 (m, 5H), 3.50 - 3.41 (m, 4H), 2.91 (s, 1H), 2.71 - 2.55 (m, 2H), 2.36 - 2.24 (m, 2H), 1.98 - 1.82 (m, 2H), 1.71 (br. s., 1H), 1.63 - 0.84 (m, 21H), 0.74 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 893.7 (M^++1).

Preparation of Compound 3100 and Compound 3101



Compound 3100



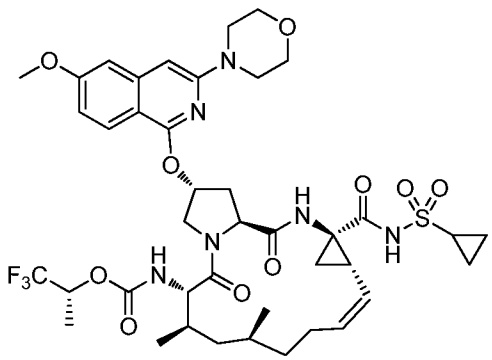
Compound 3101

Compounds 3100 and 3101 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

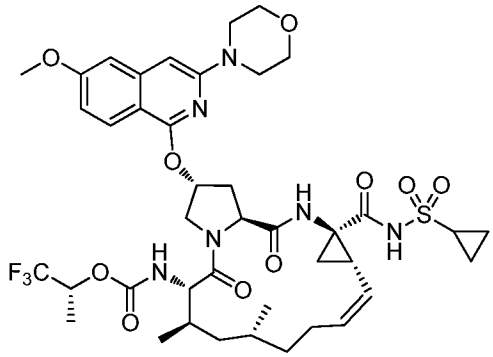
Compound 3100: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 899.8 (M^++1).

Compound 3101: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.20 (br. s., 1H), 8.95 (br. s., 1H), 7.85 (d, *J*=7.9 Hz, 1H), 7.81 (d, *J*=9.2 Hz, 1H), 7.01 (d, *J*=2.1 Hz, 1H), 6.75 (dd, *J*=8.9, 2.4 Hz, 1H), 6.46 (s, 1H), 5.75 (br. s., 1H), 5.58 - 5.45 (m, 1H), 5.18 - 5.04 (m, 1H), 4.53 - 4.38 (m, 2H), 3.93 - 3.88 (m, 1H), 3.84 (s, 3H), 3.80 - 3.73 (m, 5H), 3.51 - 3.40 (m, 4H), 2.91 (s, 1H), 2.69 - 2.55 (m, 2H), 2.36 - 2.22 (m, 2H), 1.97 - 1.80 (m, 2H), 1.77 - 1.67 (m, 1H), 1.65 - 0.85 (m, 15H), 0.73 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 899.8 (M^++1).

Preparation of Compound 3102 and Compound 3103



Compound 3102



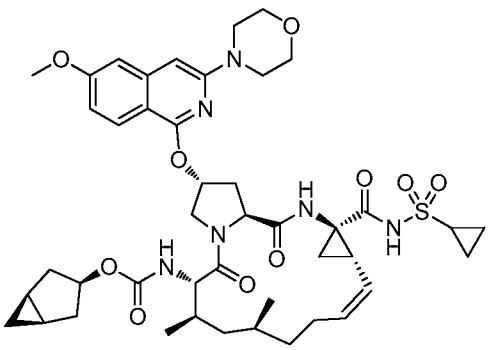
Compound 3103

Compounds 3102 and 3103 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

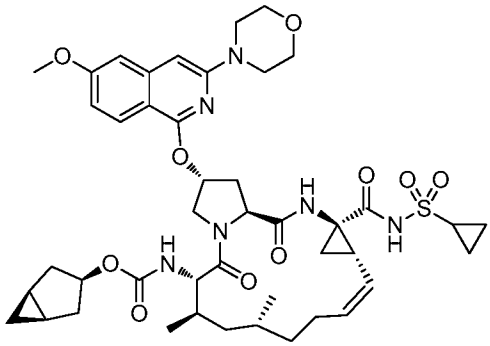
Compound 3102: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 879.7 (M^++1).

Compound 3103: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.20 (br. s., 1H), 8.91 (br. s., 1H), 8.11 (d, *J*=8.2 Hz, 1H), 7.78 (d, *J*=8.9 Hz, 1H), 7.01 (d, *J*=2.1 Hz, 1H), 6.70 (dd, *J*=9.0, 2.3 Hz, 1H), 6.46 (s, 1H), 5.75 (br. s., 1H), 5.57 - 5.47 (m, 1H), 5.14 - 5.04 (m, 1H), 5.04 - 4.93 (m, 1H), 4.49 - 4.34 (m, 2H), 3.97 - 3.90 (m, 1H), 3.86 - 3.80 (m, 4H), 3.79 - 3.75 (m, 4H), 3.53 - 3.39 (m, 4H), 2.91 (s, 1H), 2.70 - 2.55 (m, 2H), 2.35 - 2.24 (m, 2H), 2.01 - 1.84 (m, 2H), 1.77 - 1.66 (m, 1H), 1.63 - 0.81 (m, 18H), 0.75 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 879.7 (M^++1).

Preparation of Compound 3104 and Compound 3105



Compound 3104



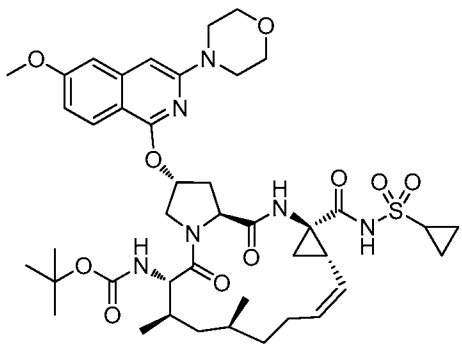
Compound 3105

Compounds 3104 and 3105 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

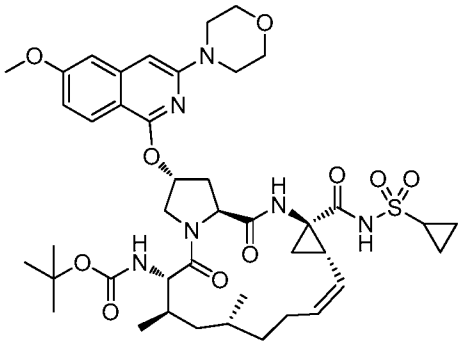
Compound 3104: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 863.8 (M^++1).

Compound 3105: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.20 (br. s., 1H), 8.89 (br. s., 1H), 7.81 (d, *J*=9.2 Hz, 1H), 7.43 (d, *J*=8.5 Hz, 1H), 7.02 (d, *J*=2.4 Hz, 1H), 6.78 (dd, *J*=9.0, 2.3 Hz, 1H), 6.47 (s, 1H), 5.75 (br. s., 1H), 5.61 - 5.44 (m, 1H), 5.23 - 4.98 (m, 1H), 4.82 (t, *J*=6.7 Hz, 1H), 4.44 - 4.34 (m, 2H), 3.96 - 3.90 (m, *J*=3.4 Hz, 1H), 3.85 (s, 3H), 3.83 - 3.73 (m, 5H), 3.52 - 3.40 (m, 4H), 2.94 - 2.86 (m, 1H), 2.63 - 2.54 (m, 2H), 2.34 - 2.22 (m, 2H), 2.08 - 1.80 (m, 4H), 1.74 - 0.84 (m, 20H), 0.72 (t, *J*=12.4 Hz, 1H), 0.47 - 0.34 (m, 2H); MS: MS *m/z* 863.8 (M^++1).

Preparation of Compound 3106 and Compound 3107



Compound 3106



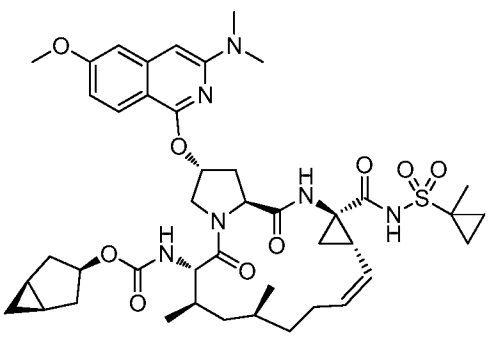
Compound 3107

Compounds 3106 and 3107 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

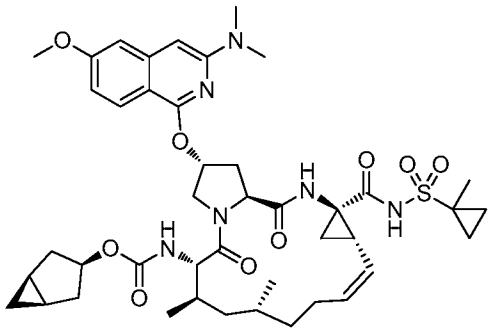
Compound 3106: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 839.7 (M^++1).

Compound 3107: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-morpholinoisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.23 (br. s., 1H), 8.93 (br. s., 1H), 7.84 (d, *J*=8.9 Hz, 1H), 7.20 (d, *J*=5.8 Hz, 1H), 7.00 (d, *J*=2.1 Hz, 1H), 6.72 (dd, *J*=9.2, 2.4 Hz, 1H), 6.45 (s, 1H), 5.73 (br. s., 1H), 5.63 - 5.44 (m, 1H), 5.20 - 5.00 (m, 1H), 4.58 - 4.45 (m, 1H), 4.42 - 4.32 (m, 1H), 3.94 - 3.87 (m, 1H), 3.84 (s, 3H), 3.81 - 3.73 (m, 5H), 3.52 - 3.39 (m, 4H), 2.95 - 2.84 (m, 1H), 2.67 - 2.55 (m, 2H), 2.34 - 2.19 (m, 2H), 2.01 - 0.84 (m, 31H), 0.71 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 839.6 (M^++1).

Preparation of Compound 3110 and Compound 3111



Compound 3110



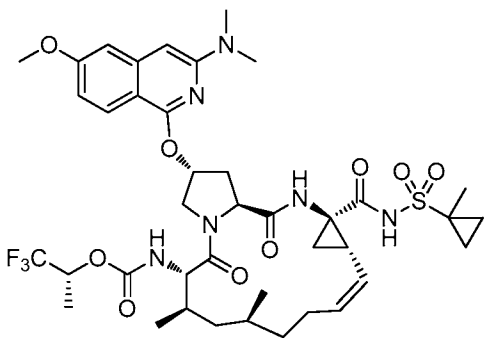
Compound 3111

Compounds 3110 and 3111 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

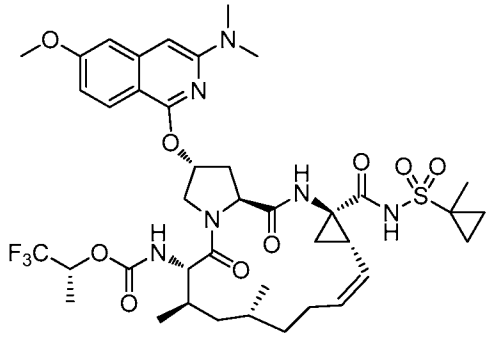
Compound 3110: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 835.6 (M^++1).

Compound 3111: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.04 (br. s., 1H), 7.76 (d, *J*=9.2 Hz, 1H), 7.45 (d, *J*=8.9 Hz, 1H), 6.96 (d, *J*=2.4 Hz, 1H), 6.68 (dd, *J*=9.0, 2.3 Hz, 1H), 6.24 (s, 1H), 5.78 (br. s., 1H), 5.60 - 5.48 (m, 1H), 5.04 - 4.94 (m, 1H), 4.81 (t, *J*=6.7 Hz, 1H), 4.47 - 4.37 (m, 2H), 3.99 (dd, *J*=11.3, 3.7 Hz, 1H), 3.87 - 3.77 (m, 4H), 3.11 - 3.05 (m, 6H), 2.74 - 2.58 (m, 2H), 2.37 - 2.24 (m, 2H), 2.08 - 1.80 (m, 4H), 1.72 - 1.09 (m, 16H), 0.97 - 0.85 (m, 8H), 0.75 (t, *J*=12.1 Hz, 1H), 0.47 - 0.32 (m, 2H); MS: MS *m/z* 835.5 (M^++1).

Preparation of Compound 3112 and Compound 3113



Compound 3112



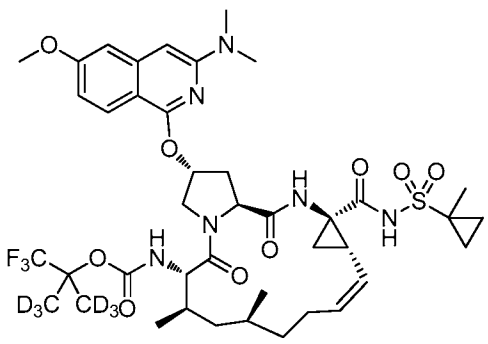
Compound 3113

Compounds 3112 and 3113 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

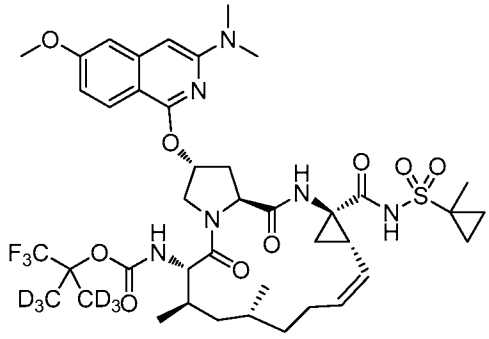
Compound 3112: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 851.5 (M^++1).

Compound 3113: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (s, 1H), 9.07 (br. s., 1H), 8.12 (d, *J*=8.2 Hz, 1H), 7.73 (d, *J*=8.9 Hz, 1H), 6.95 (d, *J*=2.4 Hz, 1H), 6.61 (dd, *J*=9.2, 2.4 Hz, 1H), 6.24 (s, 1H), 5.78 (br. s., 1H), 5.58 - 5.48 (m, 1H), 5.05 - 4.92 (m, 2H), 4.49 - 4.40 (m, 2H), 3.99 (dd, *J*=11.0, 3.7 Hz, 1H), 3.87 - 3.78 (m, 4H), 3.07 (s, 6H), 2.72 - 2.58 (m, 2H), 2.39 - 2.24 (m, 2H), 1.99 - 1.84 (m, 2H), 1.76 - 1.66 (m, 1H), 1.60 (d, *J*=5.5 Hz, 1H), 1.55 - 1.09 (m, 12H), 0.97 - 0.73 (m, 9H); MS: MS *m/z* 851.5 (M^++1).

Preparation of Compound 3114 and Compound 3115



Compound 3114



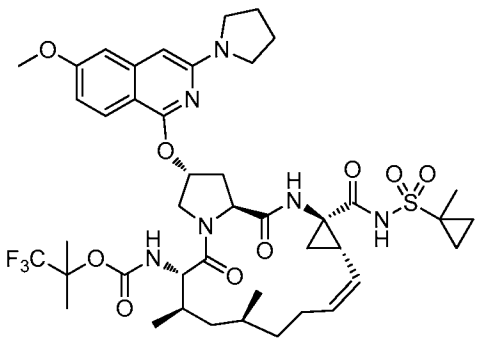
Compound 3115

Compounds 3114 and 3115 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

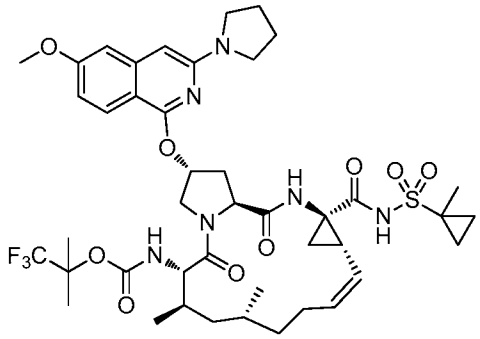
Compound 3114: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 871.6 (M^++1).

Compound 3115: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.11 (br. s., 1H), 7.86 (d, *J*=7.9 Hz, 1H), 7.76 (d, *J*=9.2 Hz, 1H), 6.95 (d, *J*=2.4 Hz, 1H), 6.65 (dd, *J*=9.0, 2.3 Hz, 1H), 6.23 (s, 1H), 5.77 (br. s., 1H), 5.53 (br. s., 1H), 5.05 - 4.90 (m, 1H), 4.53 - 4.39 (m, 2H), 3.95 (dd, *J*=11.3, 3.7 Hz, 1H), 3.83 (s, 3H), 3.76 (dd, *J*=10.7, 8.2 Hz, 1H), 3.07 (s, 6H), 2.73 - 2.58 (m, 2H), 2.40 - 2.25 (m, 2H), 1.97 - 1.81 (m, 2H), 1.76 - 1.10 (m, 11H), 0.97 - 0.84 (m, 8H), 0.76 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 871.6 (M^++1).

Preparation of Compound 3118 and Compound 3119



Compound 3118



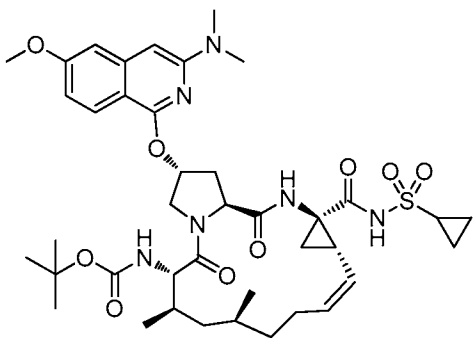
Compound 3119

Compounds 3118 and 3119 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

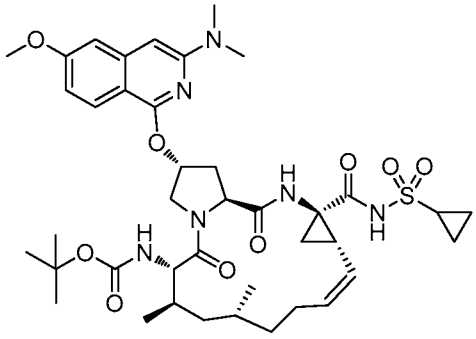
Compound 3118: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-methoxy-3-(pyrrolidin-1-yl)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 891.5 (M^++1).

Compound 3119: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-methoxy-3-(pyrrolidin-1-yl)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.11 (br. s., 1H), 7.87 (d, *J*=8.2 Hz, 1H), 7.75 (d, *J*=9.2 Hz, 1H), 6.91 (d, *J*=2.1 Hz, 1H), 6.61 (dd, *J*=9.0, 2.3 Hz, 1H), 6.05 (s, 1H), 5.76 (br. s., 1H), 5.59 - 5.49 (m, 1H), 4.97 (t, *J*=9.9 Hz, 1H), 4.51 - 4.40 (m, 2H), 3.97 (dd, *J*=11.3, 3.7 Hz, 1H), 3.83 (s, 3H), 3.77 (dd, *J*=10.7, 8.2 Hz, 1H), 3.52 - 3.39 (m, 4H), 2.75 - 2.59 (m, 2H), 2.40 - 2.24 (m, 2H), 2.04 - 1.82 (m, 6H), 1.74 - 1.66 (m, 1H), 1.65 - 1.59 (m, 1H), 1.56 - 1.23 (m, 14H), 1.20 - 1.09 (m, 1H), 0.98 - 0.86 (m, 8H), 0.76 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 891.5 (M^++1).

Preparation of Compound 3120 and Compound 3121



Compound 3120



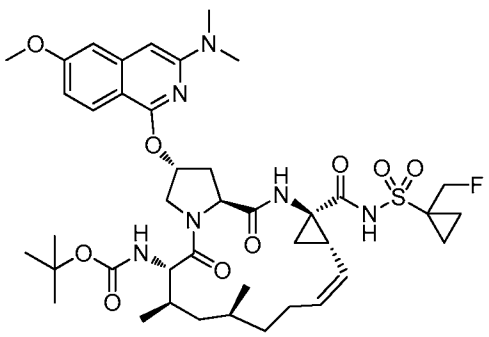
Compound 3121

Compounds 3120 and 3121 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

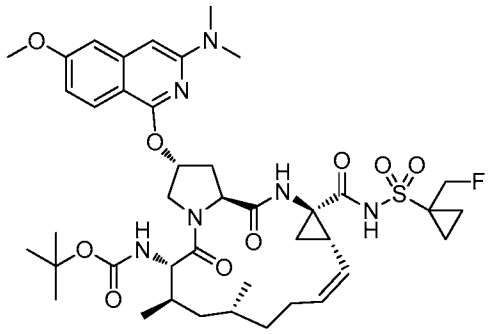
Compound 3120: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 797.5 (M^++1).

Compound 3121: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.94 (s, 1H), 7.79 (d, *J*=8.9 Hz, 1H), 7.22 (d, *J*=8.5 Hz, 1H), 6.94 (d, *J*=2.1 Hz, 1H), 6.62 (dd, *J*=8.9, 2.4 Hz, 1H), 6.23 (s, 1H), 5.75 (br. s., 1H), 5.58 - 5.48 (m, 1H), 5.05 (t, *J*=9.9 Hz, 1H), 4.49 (d, *J*=10.7 Hz, 1H), 4.43 - 4.36 (m, 1H), 3.94 (dd, *J*=11.3, 3.5 Hz, 1H), 3.83 (s, 3H), 3.77 (dd, *J*=10.5, 8.7 Hz, 1H), 3.07 (s, 6H), 2.96 - 2.88 (m, 1H), 2.73 - 2.58 (m, 2H), 2.36 - 2.23 (m, 2H), 1.98 - 1.79 (m, 2H), 1.71 (dd, *J*=12.5, 7.3 Hz, 1H), 1.64 - 1.50 (m, 2H), 1.49 - 0.85 (m, 22H), 0.73 (t, *J*=12.7 Hz, 1H); MS: MS *m/z* 797.5 (M^++1).

Preparation of Compound 3122 and Compound 3123



Compound 3122



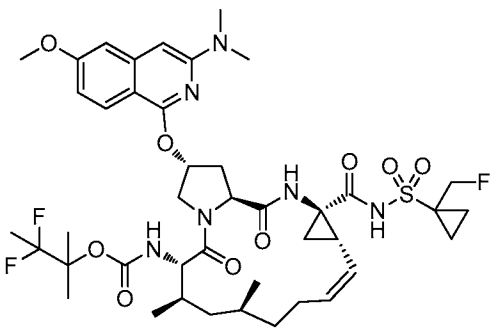
Compound 3123

Compounds 3122 and 3123 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

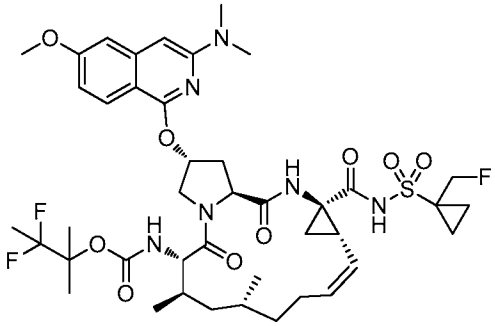
Compound 3122: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 829.5 (M^++1).

Compound 3123: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.81 (d, *J*=9.2 Hz, 1H), 6.85 (d, *J*=2.1 Hz, 1H), 6.68 (d, *J*=8.9 Hz, 1H), 6.61 (dd, *J*=9.0, 2.3 Hz, 1H), 6.19 (s, 1H), 5.82 (br. s., 1H), 5.52 (td, *J*=10.0, 6.0 Hz, 1H), 5.07 (br. s., 1H), 4.86 - 4.72 (m, 1H), 4.64 - 4.49 (m, 3H), 4.06 (dd, *J*=11.4, 3.8 Hz, 1H), 3.96 - 3.90 (m, 1H), 3.85 (s, 3H), 3.10 (s, 6H), 2.72 (dd, *J*=13.7, 7.3 Hz, 1H), 2.63 (q, *J*=9.3 Hz, 1H), 2.45 - 2.31 (m, 2H), 1.97 - 1.08 (m, 21H), 1.02 - 0.95 (m, 6H), 0.85 - 0.76 (m, 1H); MS: MS *m/z* 829.5 (M^++1).

Preparation of Compound 3124 and Compound 3125



Compound 3124



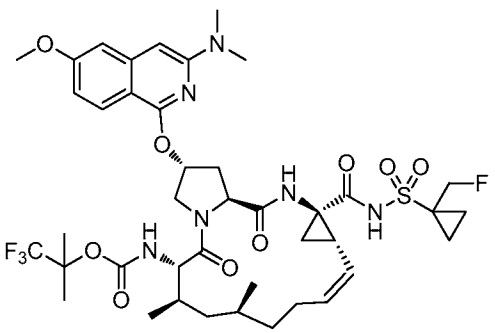
Compound 3125

Compounds 3125 and 3126 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

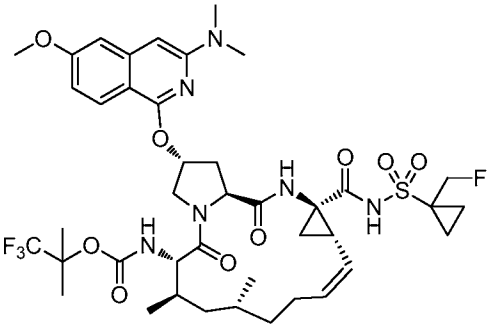
Compound 3125: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 879.5 (M^++1).

Compound 3126: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.00 (s, 1H), 7.76 (d, *J*=8.9 Hz, 1H), 7.66 (d, *J*=8.2 Hz, 1H), 6.95 (d, *J*=2.4 Hz, 1H), 6.64 (dd, *J*=9.0, 2.3 Hz, 1H), 6.24 (s, 1H), 5.77 (br. s., 1H), 5.57 - 5.45 (m, 1H), 5.01 (t, *J*=9.9 Hz, 1H), 4.88 - 4.72 (m, 1H), 4.62 - 4.47 (m, 1H), 4.46 - 4.40 (m, 2H), 3.96 (dd, *J*=11.1, 3.5 Hz, 1H), 3.83 (s, 3H), 3.77 (dd, *J*=10.4, 8.5 Hz, 1H), 3.07 (s, 6H), 2.73 - 2.58 (m, 2H), 2.36 - 2.26 (m, 2H), 1.98 - 1.79 (m, 2H), 1.75 - 1.08 (m, 19H), 0.94 (d, *J*=6.7 Hz, 3H), 0.91 (d, *J*=6.4 Hz, 3H), 0.76 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 879.5 (M^++1).

Preparation of Compound 3126 and Compound 3127



Compound 3126



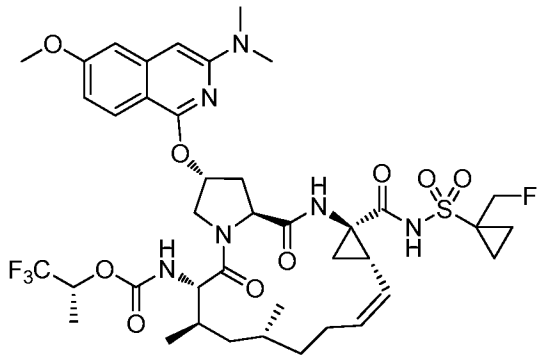
Compound 3127

Compounds 3126 and 3127 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 3126: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 883.4 (M^++1).

Compound 3127: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.81 (d, *J*=8.9 Hz, 1H), 6.87 (d, *J*=2.1 Hz, 1H), 6.64 (dd, *J*=9.0, 2.3 Hz, 1H), 6.21 (s, 1H), 5.83 (br. s., 1H), 5.57 (td, *J*=10.1, 5.8 Hz, 1H), 5.07 (t, *J*=9.5 Hz, 1H), 4.87 - 4.73 (m, 1H), 4.67 (d, *J*=11.6 Hz, 1H), 4.64 - 4.51 (m, 2H), 4.04 (dd, *J*=11.3, 3.4 Hz, 1H), 3.90 - 3.84 (m, 4H), 3.11 (s, 6H), 2.72 (dd, *J*=13.7, 7.0 Hz, 1H), 2.65 (q, *J*=9.1 Hz, 1H), 2.47 - 2.32 (m, 2H), 2.02 - 1.38 (m, 12H), 1.32 - 1.11 (m, 6H), 1.00 (d, *J*=7.0 Hz, 3H), 0.98 (d, *J*=6.4 Hz, 3H), 0.86 - 0.76 (m, 1H); MS: MS *m/z* 883.7 (M^++1).

Preparation of Compound 3128

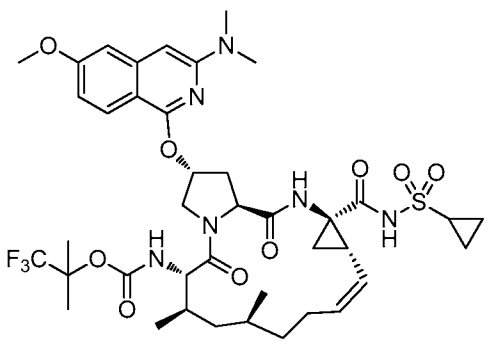


Compound 3128

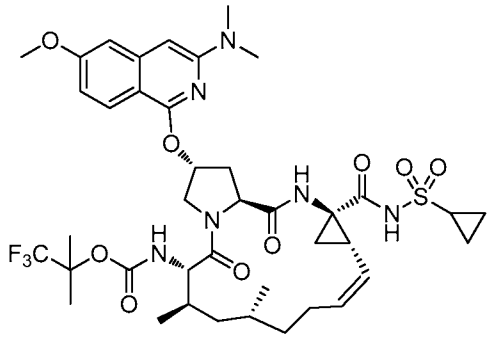
Compound 3128 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 3128: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.79 (d, *J*=8.9 Hz, 1H), 6.87 (d, *J*=2.4 Hz, 1H), 6.61 (dd, *J*=9.2, 2.4 Hz, 1H), 6.21 (s, 1H), 5.85 (br. s., 1H), 5.57 (td, *J*=10.1, 5.6 Hz, 1H), 5.03 (t, *J*=9.9 Hz, 1H), 4.86 - 4.74 (m, 2H), 4.70 - 4.48 (m, 3H), 4.04 (dd, *J*=11.3, 3.7 Hz, 1H), 3.93 (d, *J*=11.0 Hz, 1H), 3.85 (s, 3H), 3.10 (s, 6H), 2.73 (dd, *J*=13.9, 7.2 Hz, 1H), 2.65 (q, *J*=9.2 Hz, 1H), 2.47 - 2.32 (m, 2H), 2.01 - 1.85 (m, 2H), 1.79 (dd, *J*=13.3, 5.6 Hz, 1H), 1.73 - 1.37 (m, 6H), 1.30 - 1.12 (m, 6H), 1.06 - 0.94 (m, 6H), 0.91 - 0.75 (m, 1H); MS: MS *m/z* 869.5 (M^++1).

Preparation of Compound 3129 and Compound 3130



Compound 3129



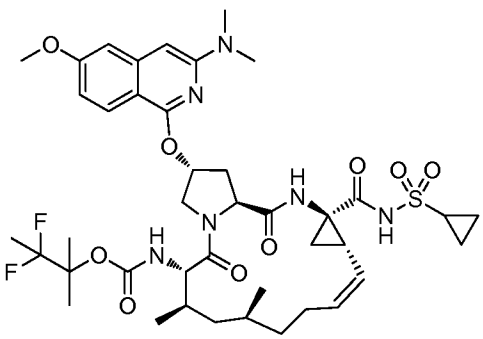
Compound 3130

Compounds 3129 and 3130 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

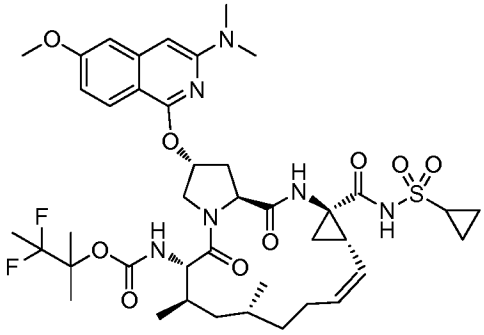
Compound 3129: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 851.1 (M^++1).

Compound 3130: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (br. s., 1H), 8.96 (br. s., 1H), 7.85 (d, *J*=8.2 Hz, 1H), 7.76 (d, *J*=8.9 Hz, 1H), 6.95 (d, *J*=2.4 Hz, 1H), 6.65 (dd, *J*=9.0, 2.3 Hz, 1H), 6.23 (s, 1H), 5.75 (br. s., 1H), 5.62 - 5.44 (m, 1H), 5.21 - 4.98 (m, 1H), 4.43 (d, *J*=8.2 Hz, 2H), 3.94 (dd, *J*=11.1, 3.5 Hz, 1H), 3.83 (s, 3H), 3.76 (dd, *J*=10.7, 8.2 Hz, 1H), 3.07 (s, 6H), 2.92 - 2.82 (m, 1H), 2.70 - 2.56 (m, 2H), 2.36 - 2.23 (m, 2H), 1.97 - 1.80 (m, 2H), 1.73 (br. s., 1H), 1.63 - 0.84 (m, 21H), 0.73 (t, *J*=11.7 Hz, 1H); MS: MS *m/z* 851.1 (M^++1).

Preparation of Compound 3131 and Compound 3132



Compound 3132



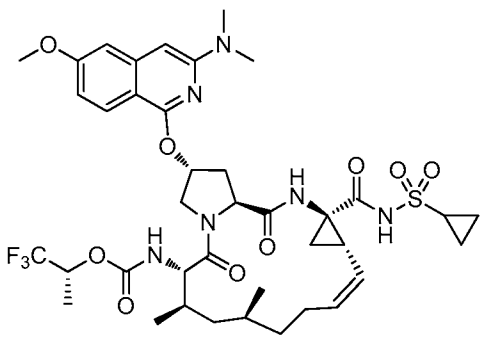
Compound 3132

Compounds 3131 and 3132 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

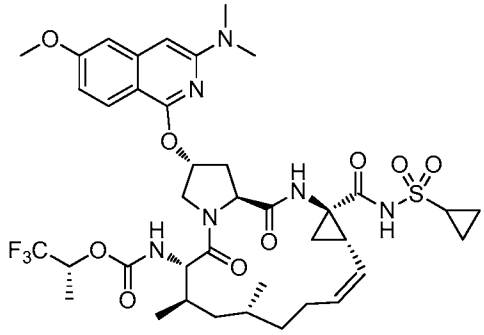
Compound 3131: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 847.1 (M^++1).

Compound 3132: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (br. s., 1H), 8.95 (br. s., 1H), 7.76 (d, *J*=9.2 Hz, 1H), 7.64 (d, *J*=7.9 Hz, 1H), 6.95 (d, *J*=2.4 Hz, 1H), 6.64 (dd, *J*=9.2, 2.4 Hz, 1H), 6.23 (s, 1H), 5.75 (br. s., 1H), 5.61 - 5.46 (m, 1H), 5.19 - 4.99 (m, 1H), 4.52 - 4.34 (m, 2H), 3.95 (dd, *J*=11.0, 3.4 Hz, 1H), 3.83 (s, 3H), 3.77 (dd, *J*=10.5, 8.7 Hz, 1H), 3.07 (s, 6H), 2.96 - 2.84 (m, 1H), 2.75 - 2.57 (m, 2H), 2.31 (ddd, *J*=13.4, 9.8, 4.0 Hz, 2H), 1.99 - 0.85 (m, 27H), 0.75 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 847.1 (M^++1).

Preparation of Compound 3133 and Compound 3134



Compound 3133



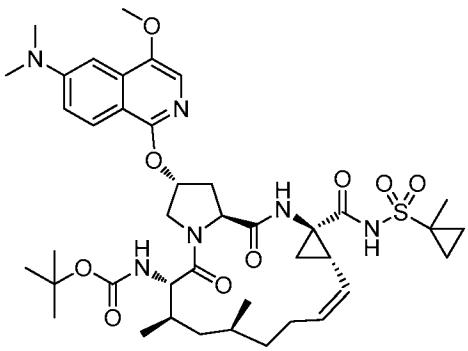
Compound 3134

Compounds 3133 and 3134 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

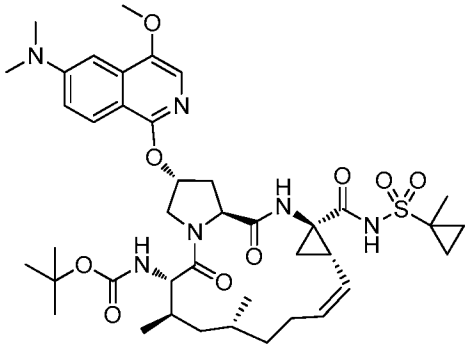
Compound 3133: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 837.4 (M^++1).

Compound 3134: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (s, 1H), 8.94 (br. s., 1H), 8.12 (d, *J*=7.9 Hz, 1H), 7.73 (d, *J*=9.2 Hz, 1H), 6.95 (d, *J*=2.4 Hz, 1H), 6.61 (dd, *J*=9.0, 2.3 Hz, 1H), 6.24 (s, 1H), 5.77 (br. s., 1H), 5.59 - 5.48 (m, 1H), 5.06 (t, *J*=9.6 Hz, 1H), 5.00 (dt, *J*=13.6, 6.9 Hz, 1H), 4.47 - 4.37 (m, 2H), 3.97 (dd, *J*=11.0, 3.4 Hz, 1H), 3.87 - 3.79 (m, 4H), 3.07 (s, 6H), 2.92 (d, *J*=8.2 Hz, 1H), 2.71 - 2.59 (m, 2H), 2.35 - 2.25 (m, 2H), 1.99 - 1.83 (m, 2H), 1.78 - 1.67 (m, 1H), 1.64 - 1.51 (m, 2H), 1.50 - 0.81 (m, 16H), 0.77 (t, *J*=11.9 Hz, 1H); MS: MS *m/z* 837.7 (M^++1).

Preparation of Compound 3135 and Compound 3136



Compound 3135



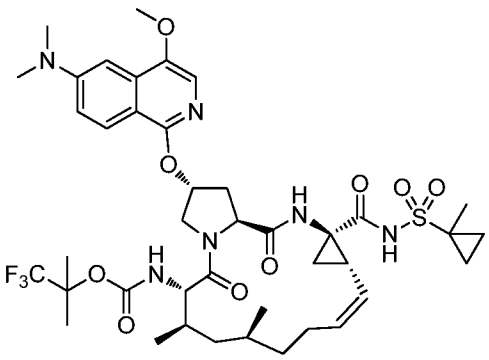
Compound 3136

Compounds 3135 and 3136 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

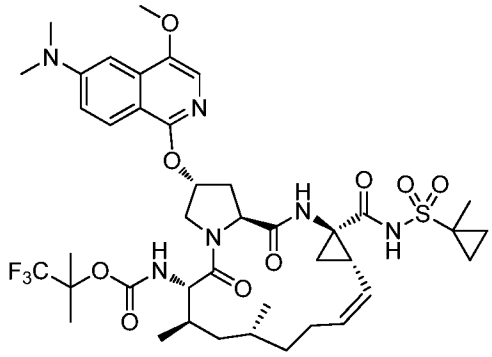
Compound 3135: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 811.6 (M^++1).

Compound 3136: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.09 (br. s., 1H), 7.91 (d, *J*=9.2 Hz, 1H), 7.44 (s, 1H), 7.18 (d, *J*=8.2 Hz, 1H), 7.08 (dd, *J*=9.2, 2.4 Hz, 1H), 6.92 (d, *J*=2.4 Hz, 1H), 5.73 (br. s., 1H), 5.59 - 5.48 (m, 1H), 5.05 - 4.92 (m, 1H), 4.56 - 4.38 (m, 2H), 3.97 - 3.87 (m, 4H), 3.79 - 3.70 (m, 1H), 3.06 (s, 6H), 2.70 (br. s., 2H), 2.43 - 2.19 (m, 2H), 1.97 - 1.78 (m, 2H), 1.70 (br. s., 1H), 1.60 (br. s., 1H), 1.54 - 1.06 (m, 18H), 0.98 - 0.84 (m, 8H), 0.73 (t, *J*=11.7 Hz, 1H); MS: MS *m/z* 811.6 (M^++1).

Preparation of Compound 3137 and Compound 3138



Compound 3137



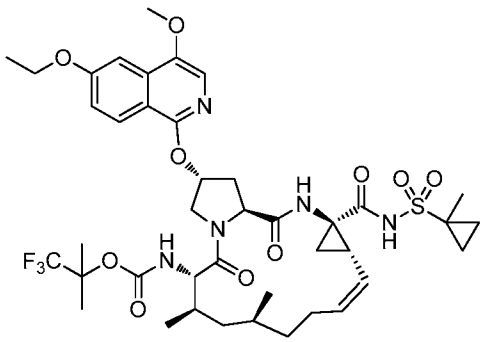
Compound 3138

Compounds 3137 and 3138 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

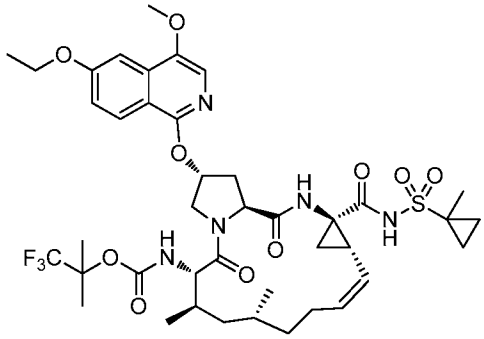
Compound 3137: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 865.6 (M^++1).

Compound 3138: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.14 (br. s., 1H), 7.88 (d, *J*=9.2 Hz, 1H), 7.83 (d, *J*=7.9 Hz, 1H), 7.45 (s, 1H), 7.11 (dd, *J*=9.3, 2.6 Hz, 1H), 6.92 (d, *J*=2.4 Hz, 1H), 5.74 (br. s., 1H), 5.58 - 5.47 (m, 1H), 5.03 - 4.93 (m, 1H), 4.54 - 4.40 (m, 2H), 3.98 - 3.86 (m, 4H), 3.72 (dd, *J*=10.7, 8.2 Hz, 1H), 3.05 (s, 6H), 2.73 - 2.54 (m, 2H), 2.42 - 2.21 (m, 2H), 1.95 - 1.81 (m, 2H), 1.76 - 1.65 (m, 1H), 1.64 - 1.57 (m, 1H), 1.55 - 1.09 (m, 15H), 0.98 - 0.84 (m, 8H), 0.75 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 865.6 (M^++1).

Preparation of Compound 3139 and Compound 3140



Compound 3139



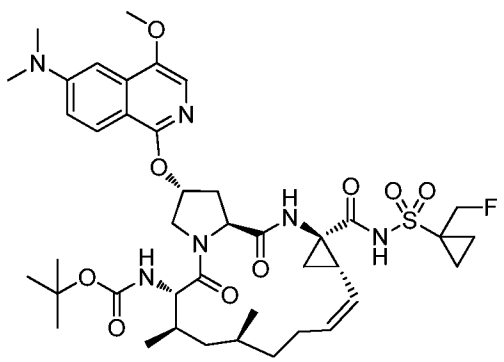
Compound 3140

Compounds 3139 and 3140 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

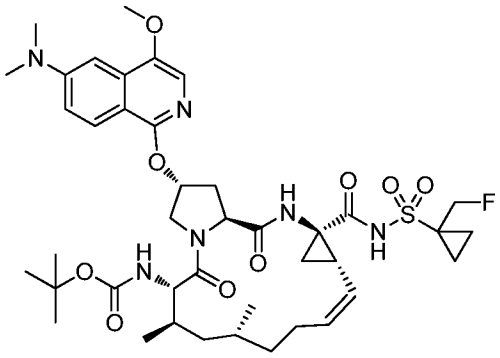
Compound 3139: MS: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS *m/z* 866.5 (M^++1).

Compound 3140: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.12 (br. s., 1H), 7.98 (d, *J*=8.9 Hz, 1H), 7.82 (d, *J*=7.6 Hz, 1H), 7.60 (s, 1H), 7.32 (d, *J*=2.4 Hz, 1H), 7.18 (dd, *J*=9.2, 2.4 Hz, 1H), 5.74 (br. s., 1H), 5.57 - 5.45 (m, 1H), 5.10 - 4.93 (m, 1H), 4.55 - 4.40 (m, 2H), 4.19 (q, *J*=7.0 Hz, 2H), 3.96 (s, 3H), 3.93 - 3.87 (m, 1H), 3.71 (dd, *J*=10.5, 8.1 Hz, 1H), 2.70 - 2.54 (m, 2H), 2.37 - 2.23 (m, 2H), 1.94 - 1.08 (m, 22H), 0.98 - 0.84 (m, 8H), 0.73 (br. s., 1H); MS: MS *m/z* 866.5 (M^++1).

Preparation of Compound 3141 and Compound 3142



Compound 3141



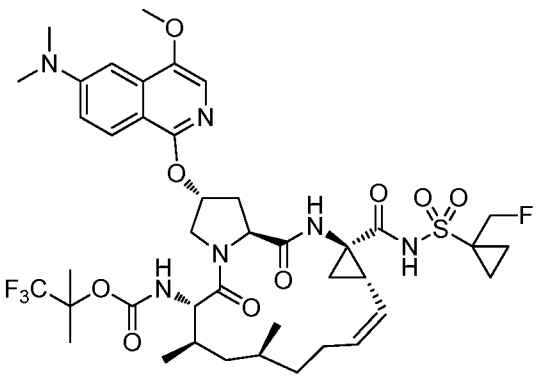
Compound 3142

Compounds 3141 and 3142 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

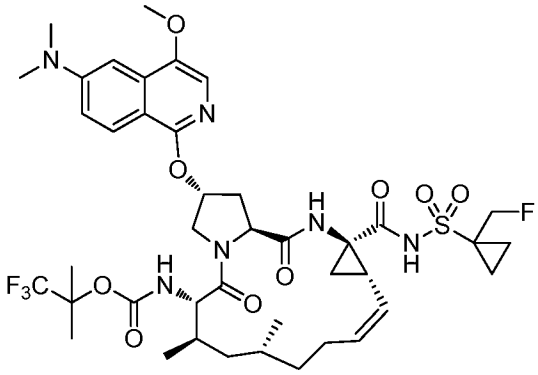
Compound 3141: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 829.6 (M^++1).

Compound 3142: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.01 (br. s., 1H), 7.91 (d, *J*=9.2 Hz, 1H), 7.45 (s, 1H), 7.19 (d, *J*=7.9 Hz, 1H), 7.08 (dd, *J*=9.0, 2.3 Hz, 1H), 6.92 (d, *J*=2.4 Hz, 1H), 5.71 (br. s., 1H), 5.59 - 5.45 (m, 1H), 4.99 (t, *J*=9.8 Hz, 1H), 4.90 - 4.72 (m, 1H), 4.64 - 4.36 (m, 3H), 3.96 - 3.86 (m, 4H), 3.80 - 3.71 (m, 1H), 3.06 (s, 6H), 2.73 - 2.54 (m, 2H), 2.37 - 2.20 (m, 2H), 1.97 - 1.77 (m, 2H), 1.74 - 1.65 (m, 1H), 1.61 - 1.04 (m, 18H), 0.94 (d, *J*=7.0 Hz, 3H), 0.89 (d, *J*=6.4 Hz, 3H), 0.73 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 829.6 (M^++1).

Preparation of Compound 3143 and Compound 3144



Compound 3143



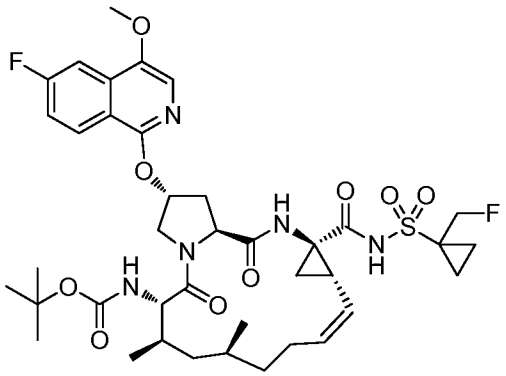
Compound 3144

Compounds 3143 and 3144 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

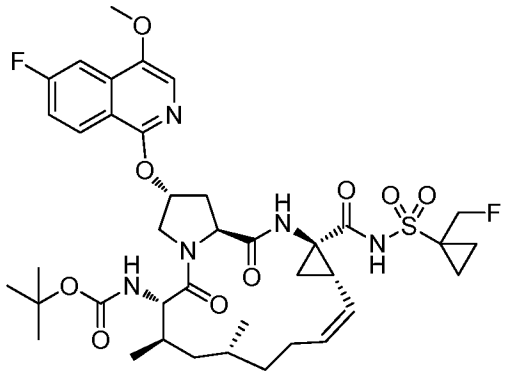
Compound 3143: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 883.6 (M^++1).

Compound 3144: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.05 (s, 1H), 7.88 (d, *J*=9.2 Hz, 1H), 7.83 (d, *J*=7.9 Hz, 1H), 7.46 (s, 1H), 7.11 (dd, *J*=9.2, 2.4 Hz, 1H), 6.92 (d, *J*=2.4 Hz, 1H), 5.73 (br. s., 1H), 5.58 - 5.46 (m, 1H), 4.99 (t, *J*=9.9 Hz, 1H), 4.90 - 4.73 (m, 1H), 4.63 - 4.41 (m, 3H), 3.96 - 3.86 (m, 4H), 3.73 (dd, *J*=10.5, 8.4 Hz, 1H), 3.06 (s, 6H), 2.66 (q, *J*=9.1 Hz, 1H), 2.59 (dd, *J*=13.6, 6.6 Hz, 1H), 2.40 - 2.21 (m, 2H), 1.94 - 1.79 (m, 2H), 1.70 (dd, *J*=12.8, 6.4 Hz, 1H), 1.60 - 1.08 (m, 15H), 0.94 (d, *J*=7.0 Hz, 3H), 0.89 (d, *J*=6.4 Hz, 3H), 0.74 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 883.6 (M^++1).

Preparation of Compound 3145 and Compound 3146



Compound 3145



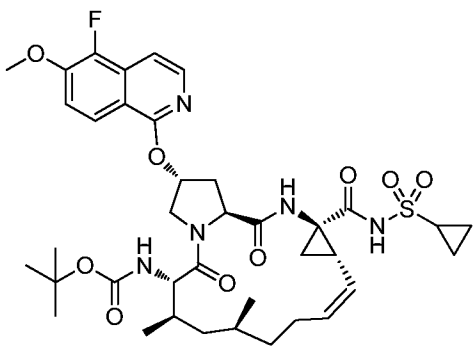
Compound 3146

Compounds 3145 and 3146 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

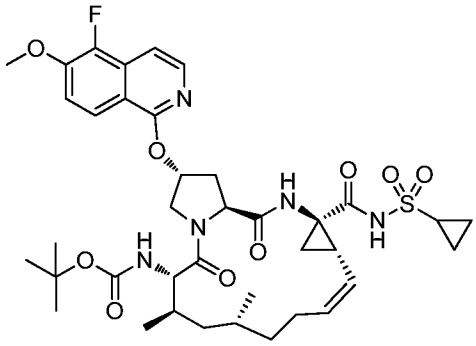
Compound 3145: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-fluoro-4-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 804.4 (M^++1).

Compound 3146: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-fluoro-4-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.30 (br. s., 1H), 9.05 (br. s., 1H), 8.17 (dd, *J*=9.2, 5.8 Hz, 1H), 7.74 - 7.66 (m, 2H), 7.48 (td, *J*=8.9, 2.4 Hz, 1H), 7.16 (br. s., 1H), 5.76 (br. s., 1H), 5.59 - 5.46 (m, 1H), 5.07 - 4.92 (m, 1H), 4.91 - 4.71 (m, 1H), 4.68 - 4.40 (m, 3H), 3.97 (s, 3H), 3.89 (dd, *J*=11.7, 3.2 Hz, 1H), 3.68 (dd, *J*=10.5, 8.7 Hz, 1H), 2.73 - 2.56 (m, 2H), 2.36 - 2.22 (m, 2H), 1.95 - 1.64 (m, 3H), 1.62 - 1.01 (m, 18H), 0.93 (d, *J*=6.7 Hz, 3H), 0.87 (d, *J*=6.4 Hz, 3H), 0.77 - 0.65 (m, 1H); MS: MS *m/z* 804.4 (M^++1).

Preparation of Compound 3147 and Compound 3148



Compound 3147



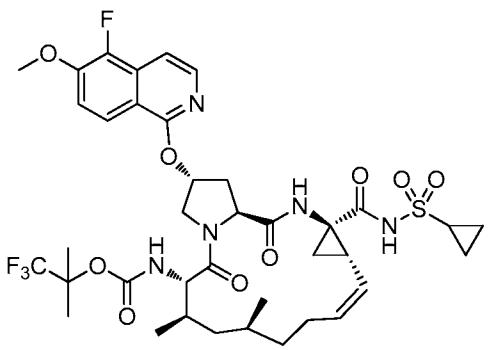
Compound 3148

Compounds 3147 and 3148 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

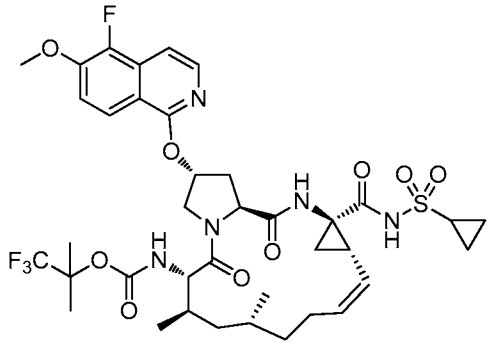
Compound 3147: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((5-fluoro-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 772.5 (M^++1).

Compound 3148: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((5-fluoro-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (br. s., 1H), 9.01 (br. s., 1H), 8.03 (d, *J*=6.1 Hz, 1H), 7.99 - 7.92 (m, 1H), 7.49 (t, *J*=8.7 Hz, 1H), 7.38 (d, *J*=5.8 Hz, 1H), 7.15 (d, *J*=7.9 Hz, 1H), 5.83 (br. s., 1H), 5.59 - 5.45 (m, 1H), 5.16 - 5.00 (m, 1H), 4.61 (d, *J*=11.0 Hz, 1H), 4.48 (dd, *J*=9.8, 7.3 Hz, 1H), 4.01 (s, 3H), 3.89 (dd, *J*=11.3, 3.4 Hz, 1H), 3.68 (dd, *J*=10.5, 8.4 Hz, 1H), 2.96 - 2.86 (m, 1H), 2.73 - 2.57 (m, 2H), 2.37 - 2.23 (m, 2H), 1.91 (d, *J*=9.8 Hz, 1H), 1.85 - 1.75 (m, 1H), 1.69 (br. s., 1H), 1.64 - 1.50 (m, 2H), 1.47 - 0.80 (m, 22H), 0.71 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 772.5 (M^++1).

Preparation of Compound 3149 and Compound 3150



Compound 3149



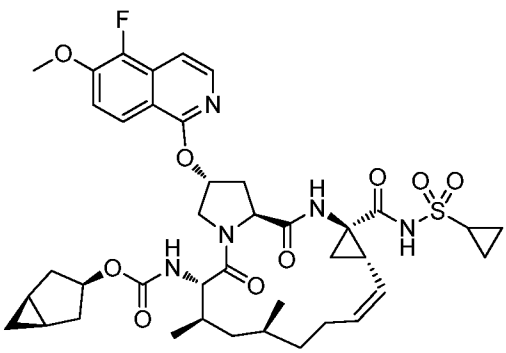
Compound 3150

Compounds 3149 and 3150 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

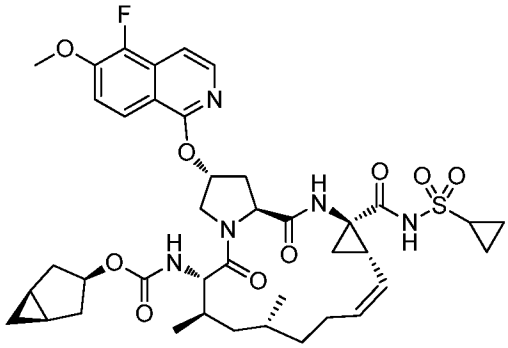
Compound 3149: MS: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((5-fluoro-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS *m/z* 826.5 (M^++1).

Compound 3150: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((5-fluoro-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, METHANOL-d_4) δ 8.05 - 7.96 (m, 2H), 7.45 - 7.36 (m, 2H), 5.88 (t, *J*=3.4 Hz, 1H), 5.59 (td, *J*=10.2, 5.8 Hz, 1H), 5.14 (br. s., 1H), 4.74 (d, *J*=11.0 Hz, 1H), 4.68 - 4.58 (m, 2H), 4.03 (s, 3H), 4.01 (dd, *J*=11.7, 3.2 Hz, 1H), 3.79 (d, *J*=10.7 Hz, 1H), 2.96 - 2.89 (m, 1H), 2.74 (dd, *J*=14.0, 7.0 Hz, 1H), 2.70 - 2.60 (m, 1H), 2.50 - 2.33 (m, 2H), 2.01 - 1.91 (m, 1H), 1.90 - 1.73 (m, 3H), 1.58 (dd, *J*=9.6, 5.3 Hz, 1H), 1.53 - 1.41 (m, 2H), 1.37 - 1.17 (m, 5H), 1.13 - 1.04 (m, 2H), 1.04 - 0.91 (m, 9H), 0.85 - 0.77 (m, 1H); MS: MS *m/z* 826.5 (M^++1).

Preparation of Compound 3151 and Compound 3152



Compound 3151



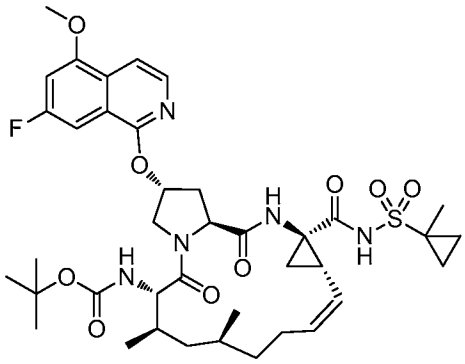
Compound 3152

Compounds 3151 and 3152 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

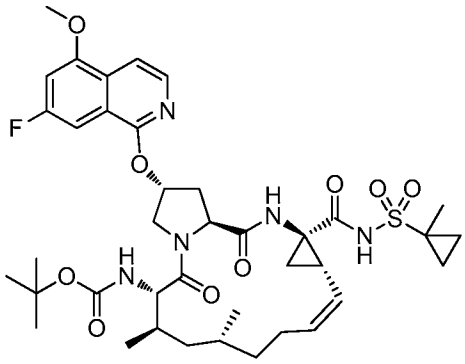
Compound 3151: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((5-fluoro-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 796.5 (M^++1).

Compound 3152: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((5-fluoro-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, METHANOL-d_4) δ 8.04 - 7.95 (m, 2H), 7.48 - 7.37 (m, 2H), 5.90 (br. s., 1H), 5.56 (td, *J*=10.1, 6.1 Hz, 1H), 5.18 (br. s., 1H), 4.66 - 4.58 (m, 3H), 4.51 (t, *J*=6.9 Hz, 1H), 4.06 - 3.99 (m, 4H), 3.88 (d, *J*=11.0 Hz, 1H), 2.94 - 2.88 (m, 1H), 2.73 (dd, *J*=13.7, 7.0 Hz, 1H), 2.68 - 2.58 (m, 1H), 2.44 (ddd, *J*=13.7, 10.1, 4.3 Hz, 1H), 2.40 - 2.31 (m, 1H), 2.01 - 1.92 (m, 2H), 1.86 (d, *J*=6.1 Hz, 1H), 1.78 - 1.69 (m, 3H), 1.64 (d, *J*=14.6 Hz, 1H), 1.58 (dd, *J*=9.5, 5.2 Hz, 1H), 1.52 - 0.90 (m, 15H), 0.84 - 0.75 (m, 1H), 0.38 - 0.29 (m, 1H), 0.26 (q, *J*=4.2 Hz, 1H); MS: MS *m/z* 796.5 (M^++1).

Preparation of Compound 3153 and Compound 3154



Compound 3153



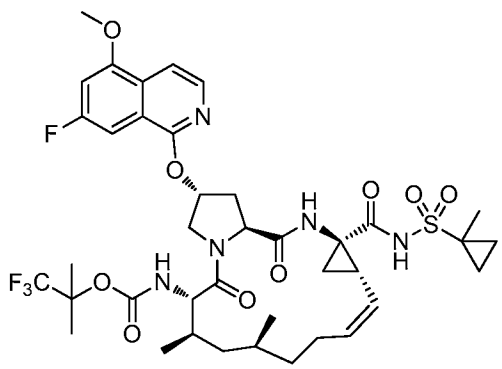
Compound 3154

Compounds 3153 and 3154 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

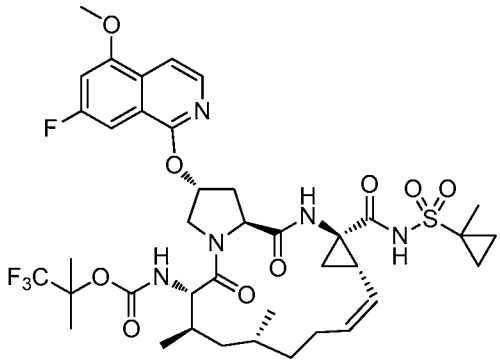
Compound 3153: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 786.6 (M^++1).

Compound 3154: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.09 (br. s., 1H), 8.01 (d, *J*=6.1 Hz, 1H), 7.51 (d, *J*=6.1 Hz, 1H), 7.28 (dd, *J*=9.2, 1.8 Hz, 1H), 7.21 (dd, *J*=11.3, 2.1 Hz, 1H), 7.17 (d, *J*=7.6 Hz, 1H), 5.82 (br. s., 1H), 5.58 - 5.45 (m, 1H), 5.11 - 4.90 (m, 1H), 4.61 (d, *J*=10.7 Hz, 1H), 4.49 (t, *J*=6.9 Hz, 1H), 4.01 (s, 3H), 3.94 - 3.87 (m, 1H), 3.68 (dd, *J*=10.7, 8.2 Hz, 1H), 2.74 - 2.55 (m, 2H), 2.40 - 2.25 (m, 2H), 1.97 - 1.04 (m, 24H), 0.93 (d, *J*=7.0 Hz, 3H), 0.88 (d, *J*=6.4 Hz, 3H), 0.73 (t, *J*=12.7 Hz, 1H); MS: MS *m/z* 786.6 (M^++1).

Preparation of Compound 3155 and Compound 3156



Compound 3155



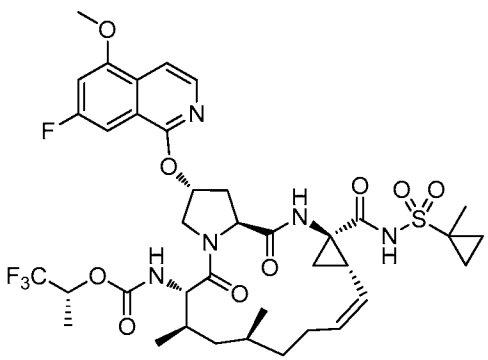
Compound 3156

Compounds 3155 and 3156 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

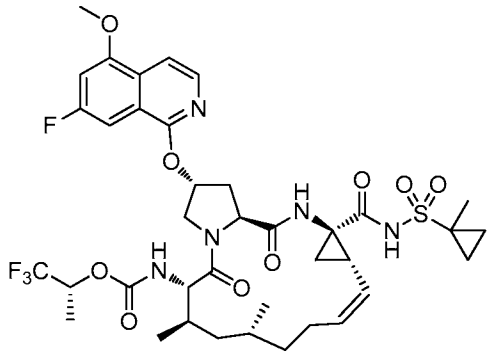
Compound 3155: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 840.7 (M^++1).

Compound 3156: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.02 (br. s., 1H), 9.11 (br. s., 1H), 8.02 (d, *J*=6.1 Hz, 1H), 7.83 (d, *J*=6.4 Hz, 1H), 7.52 (d, *J*=5.8 Hz, 1H), 7.31 - 7.26 (m, 1H), 7.23 (dd, *J*=11.1, 2.3 Hz, 1H), 5.82 (br. s., 1H), 5.61 - 5.45 (m, 1H), 5.10 - 4.87 (m, 1H), 4.63 - 4.45 (m, 2H), 4.01 (s, 3H), 3.94 - 3.88 (m, 1H), 3.69 (dd, *J*=10.7, 8.2 Hz, 1H), 2.73 - 2.56 (m, 2H), 2.37 - 2.23 (m, 2H), 1.95 - 0.83 (m, 27H), 0.80 - 0.69 (m, 1H); MS: MS *m/z* 840.7 (M^++1).

Preparation of Compound 3157 and Compound 3158



Compound 3157



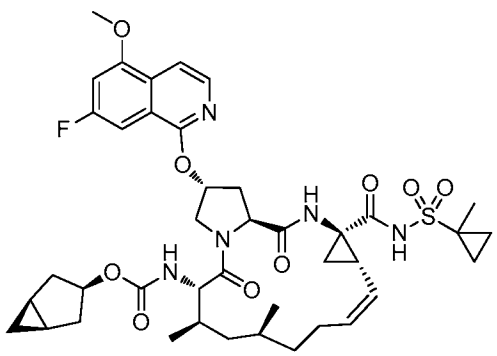
Compound 3158

Compounds 3157 and 3158 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

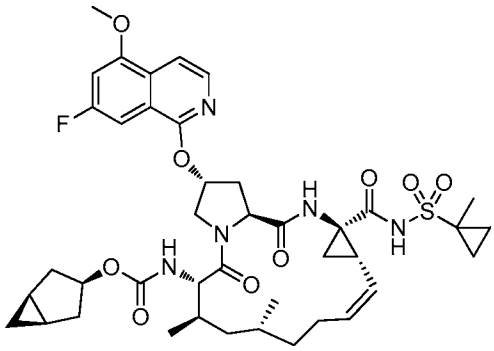
Compound 3157: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 826.6 (M^++1).

Compound 3158: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.01 (br. s., 1H), 9.07 (br. s., 1H), 8.12 (d, *J*=7.6 Hz, 1H), 8.01 (d, *J*=6.1 Hz, 1H), 7.52 (d, *J*=6.1 Hz, 1H), 7.36 (dd, *J*=9.5, 2.1 Hz, 1H), 7.22 (dd, *J*=11.3, 2.1 Hz, 1H), 5.81 (br. s., 1H), 5.59 - 5.47 (m, 1H), 5.07 - 4.94 (m, 1H), 4.78 (quin, *J*=6.9 Hz, 1H), 4.56 (d, *J*=11.0 Hz, 1H), 4.52 - 4.43 (m, 1H), 4.01 (s, 3H), 3.95 - 3.88 (m, 1H), 3.78 (dd, *J*=10.7, 7.9 Hz, 1H), 2.66 (br. s., 2H), 2.35 - 2.24 (m, 2H), 1.98 - 1.81 (m, 2H), 1.74 - 1.66 (m, 1H), 1.64 - 1.57 (m, 1H), 1.56 - 1.49 (m, 1H), 1.49 - 1.07 (m, 11H), 0.98 - 0.85 (m, 8H), 0.78 (t, *J*=11.3 Hz, 1H); MS: MS *m/z* 826.6 (M^++1).

Preparation of Compound 3159 and Compound 3160



Compound 3159



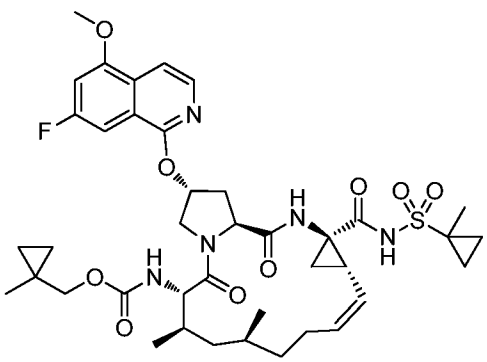
Compound 3160

Compounds 3159 and 3160 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

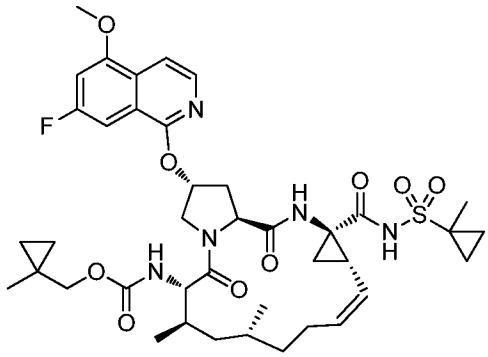
Compound 3159: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 810.7 (M^++1).

Compound 3160: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.03 (br. s., 1H), 8.01 (d, *J*=6.1 Hz, 1H), 7.52 (d, *J*=6.1 Hz, 1H), 7.41 (br. s., 1H), 7.35 (dd, *J*=9.3, 2.0 Hz, 1H), 7.24 (dd, *J*=11.3, 2.1 Hz, 1H), 5.82 (br. s., 1H), 5.60 - 5.43 (m, 1H), 5.06 - 4.93 (m, 1H), 4.70 (t, *J*=6.9 Hz, 1H), 4.59 - 4.40 (m, 2H), 4.02 (s, 3H), 3.96 - 3.89 (m, 1H), 3.74 (dd, *J*=10.7, 8.5 Hz, 1H), 2.74 - 2.56 (m, 2H), 2.36 - 2.23 (m, 2H), 2.01 - 1.07 (m, 19H), 0.97 - 0.82 (m, 8H), 0.74 (br. s., 1H), 0.42 - 0.30 (m, 2H); MS: MS *m/z* 810.7 (M^++1).

Preparation of Compound 3161 and Compound 3162



Compound 3161



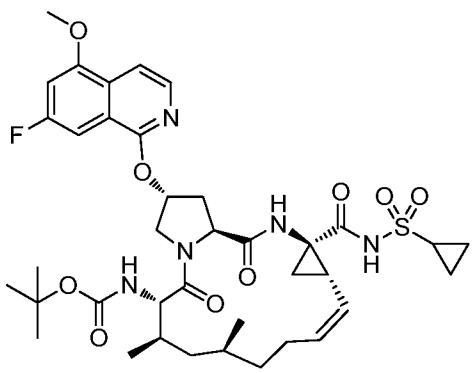
Compound 3162

Compounds 3161 and 3162 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

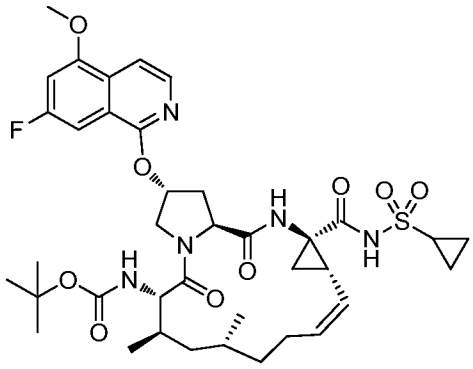
Compound 3161: (1-methylcyclopropyl)methyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 798.7 (M^++1).

Compound 3162: (1-methylcyclopropyl)methyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.04 (br. s., 1H), 8.00 (d, *J*=6.1 Hz, 1H), 7.54 (d, *J*=6.4 Hz, 1H), 7.51 (d, *J*=6.1 Hz, 1H), 7.38 (dd, *J*=9.5, 2.1 Hz, 1H), 7.23 (dd, *J*=11.3, 2.1 Hz, 1H), 5.80 (br. s., 1H), 5.62 - 5.46 (m, 1H), 5.10 - 4.91 (m, 1H), 4.58 (d, *J*=9.8 Hz, 1H), 4.51 - 4.39 (m, 1H), 4.01 (s, 3H), 3.95 - 3.88 (m, 1H), 3.75 (dd, *J*=10.7, 8.2 Hz, 1H), 3.55 - 3.43 (m, 2H), 2.64 (d, *J*=15.9 Hz, 2H), 2.36 - 2.21 (m, 2H), 1.99 - 0.84 (m, 24H), 0.75 (t, *J*=11.9 Hz, 1H), 0.35 - 0.15 (m, 4H); MS: MS *m/z* 798.7 (M^++1).

Preparation of Compound 3163 and Compound 3164



Compound 3163



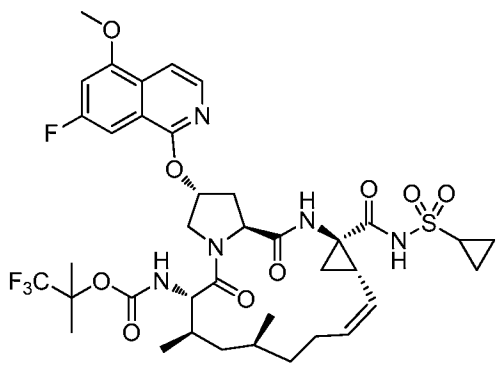
Compound 3164

Compounds 3163 and 3164 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

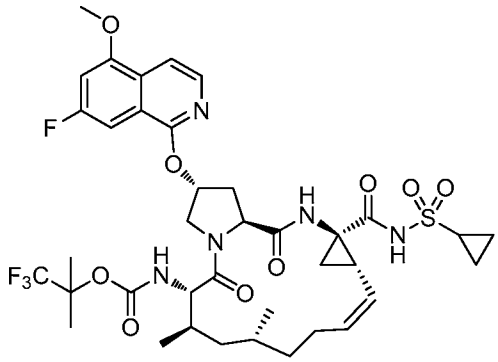
Compound 3163: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 772.7 (M^++1).

Compound 3164: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (br. s., 1H), 8.96 (br. s., 1H), 8.01 (d, *J*=5.8 Hz, 1H), 7.51 (d, *J*=5.8 Hz, 1H), 7.31 - 7.25 (m, 1H), 7.23 - 7.14 (m, 2H), 5.80 (br. s., 1H), 5.56 - 5.45 (m, 1H), 5.12 - 5.00 (m, 1H), 4.60 (d, *J*=7.9 Hz, 1H), 4.51 - 4.39 (m, 1H), 4.01 (s, 3H), 3.88 (dd, *J*=11.1, 2.9 Hz, 1H), 3.68 (dd, *J*=10.4, 8.5 Hz, 1H), 2.96 - 2.83 (m, 1H), 2.74 - 2.56 (m, 2H), 2.38 - 2.24 (m, 2H), 1.96 - 0.81 (m, 27H), 0.72 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 772.7 (M^++1).

Preparation of Compound 3165 and Compound 3166



Compound 3165



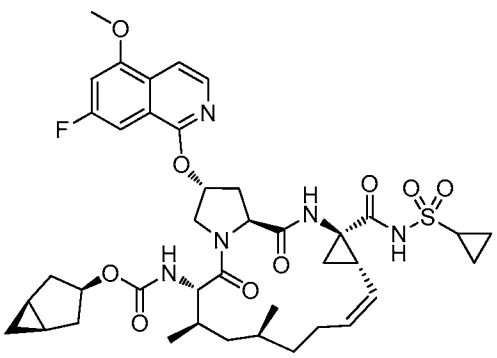
Compound 3166

Compounds 3165 and 3166 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

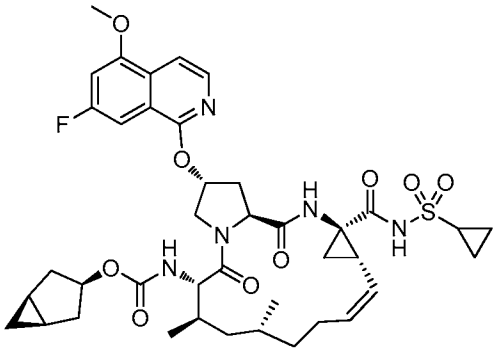
Compound 3165: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 826.6 (M^++1).

Compound 3166: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.99 (br. s., 1H), 8.02 (d, *J*=6.1 Hz, 1H), 7.85 (d, *J*=7.6 Hz, 1H), 7.52 (d, *J*=6.1 Hz, 1H), 7.28 (dd, *J*=9.3, 2.0 Hz, 1H), 7.23 (dd, *J*=11.3, 2.1 Hz, 1H), 5.81 (br. s., 1H), 5.58 - 5.48 (m, 1H), 5.06 (t, *J*=9.8 Hz, 1H), 4.61 - 4.44 (m, 2H), 4.01 (s, 3H), 3.89 (dd, *J*=11.4, 3.2 Hz, 1H), 3.69 (dd, *J*=10.7, 7.9 Hz, 1H), 2.96 - 2.87 (m, 1H), 2.72 - 2.59 (m, 2H), 2.37 - 2.27 (m, 2H), 1.96 - 1.79 (m, 2H), 1.77 - 1.68 (m, 1H), 1.65 - 1.53 (m, 2H), 1.51 - 0.96 (m, 13H), 0.94 (d, *J*=7.0 Hz, 3H), 0.90 (d, *J*=6.4 Hz, 3H), 0.75 (t, *J*=12.7 Hz, 1H); MS: MS *m/z* 826.6 (M^++1).

Preparation of Compound 3167 and Compound 3168



Compound 3167



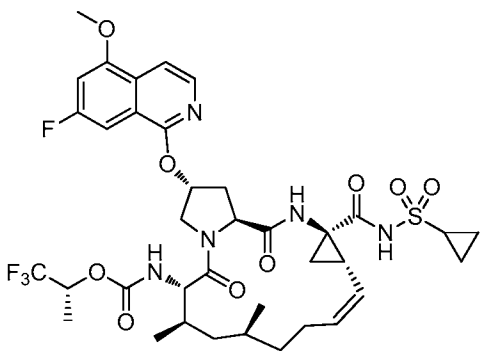
Compound 3168

Compounds 3167 and 3168 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

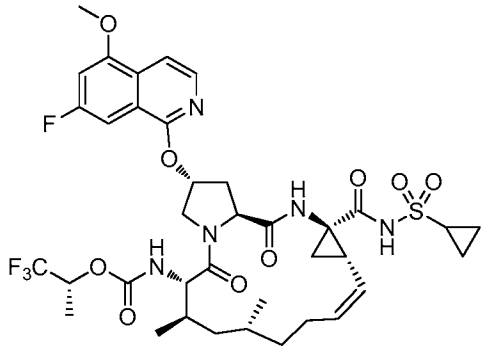
Compound 3167: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 796.5 (M^++1).

Compound 3168: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.91 (br. s., 1H), 8.01 (d, *J*=5.8 Hz, 1H), 7.52 (d, *J*=5.8 Hz, 1H), 7.43 (d, *J*=7.9 Hz, 1H), 7.38 - 7.32 (m, 1H), 7.24 (dd, *J*=11.3, 2.1 Hz, 1H), 5.81 (br. s., 1H), 5.59 - 5.47 (m, 1H), 5.07 (t, *J*=9.8 Hz, 1H), 4.72 (t, *J*=6.9 Hz, 1H), 4.53 (d, *J*=11.3 Hz, 1H), 4.48 - 4.40 (m, 1H), 4.02 (s, 3H), 3.90 (dd, *J*=11.1, 2.9 Hz, 1H), 3.74 (dd, *J*=10.5, 8.7 Hz, 1H), 2.96 - 2.88 (m, 1H), 2.74 - 2.58 (m, 2H), 2.35 - 2.24 (m, 2H), 2.00 - 1.89 (m, 2H), 1.88 - 1.75 (m, 2H), 1.73 - 0.96 (m, 14H), 0.93 (d, *J*=7.0 Hz, 3H), 0.88 (d, *J*=6.4 Hz, 3H), 0.74 (t, *J*=12.4 Hz, 1H), 0.41 - 0.32 (m, 2H); MS: MS *m/z* 796.5 (M^++1).

Preparation of Compound 3169 and Compound 3170



Compound 3169



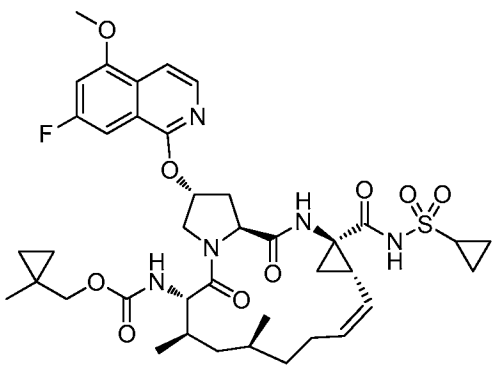
Compound 3170

Compounds 3169 and 3170 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

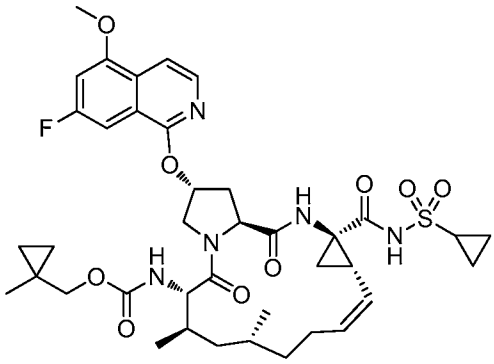
Compound 3169: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 812.5 (M^++1).

Compound 3170: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.16 (s, 1H), 8.94 (s, 1H), 8.12 (d, *J*=7.6 Hz, 1H), 8.01 (d, *J*=5.8 Hz, 1H), 7.52 (d, *J*=5.8 Hz, 1H), 7.37 (dd, *J*=9.5, 2.1 Hz, 1H), 7.22 (dd, *J*=11.1, 2.3 Hz, 1H), 5.79 (br. s., 1H), 5.57 - 5.47 (m, 1H), 5.07 (t, *J*=9.6 Hz, 1H), 4.81 (dt, *J*=13.5, 6.8 Hz, 1H), 4.55 (d, *J*=11.0 Hz, 1H), 4.44 (dd, *J*=10.2, 7.2 Hz, 1H), 4.01 (s, 3H), 3.90 (dd, *J*=11.1, 2.9 Hz, 1H), 3.78 (dd, *J*=10.5, 7.8 Hz, 1H), 2.96 - 2.87 (m, 1H), 2.70 - 2.59 (m, 2H), 2.36 - 2.24 (m, 2H), 2.02 - 1.81 (m, 2H), 1.77 - 1.66 (m, 1H), 1.64 - 1.52 (m, 2H), 1.50 - 1.31 (m, 2H), 1.23 (d, *J*=6.7 Hz, 3H), 1.20 - 0.86 (m, 11H), 0.77 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 812.4 (M^++1).

Preparation of Compound 3171 and Compound 3172



Compound 3171



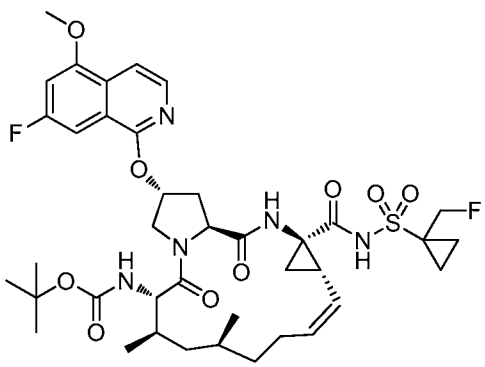
Compound 3172

Compounds 3171 and 3172 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

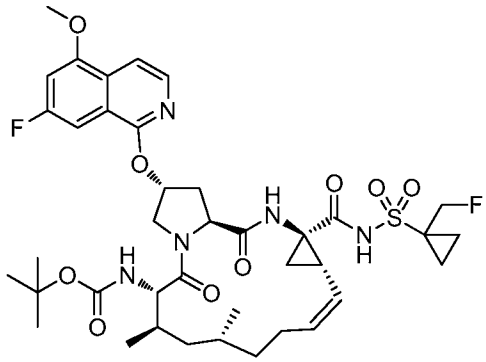
Compound 3171: (1-methylcyclopropyl)methyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 784.5 (M^++1).

Compound 3172: (1-methylcyclopropyl)methyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.17 (br. s., 1H), 8.91 (br. s., 1H), 8.00 (d, *J*=6.1 Hz, 1H), 7.55 (d, *J*=7.6 Hz, 1H), 7.51 (d, *J*=6.1 Hz, 1H), 7.39 (dd, *J*=9.6, 2.0 Hz, 1H), 7.23 (dd, *J*=11.3, 2.1 Hz, 1H), 5.79 (br. s., 1H), 5.57 - 5.47 (m, 1H), 5.13 - 5.01 (m, 1H), 4.59 (d, *J*=11.0 Hz, 1H), 4.49 - 4.37 (m, 1H), 4.01 (s, 3H), 3.89 (dd, *J*=11.3, 3.1 Hz, 1H), 3.75 (dd, *J*=10.4, 8.2 Hz, 1H), 3.55 - 3.44 (m, 2H), 2.91 (s, 1H), 2.64 (d, *J*=12.8 Hz, 2H), 2.35 - 2.23 (m, 2H), 1.99 - 1.79 (m, 2H), 1.71 (br. s., 1H), 1.64 - 1.51 (m, 2H), 1.49 - 1.32 (m, 2H), 1.25 - 0.88 (m, 14H), 0.75 (t, *J*=12.1 Hz, 1H), 0.36 - 0.18 (m, 4H); MS: MS *m/z* 784.5 (M^++1).

Preparation of Compound 3173 and Compound 3174



Compound 3173



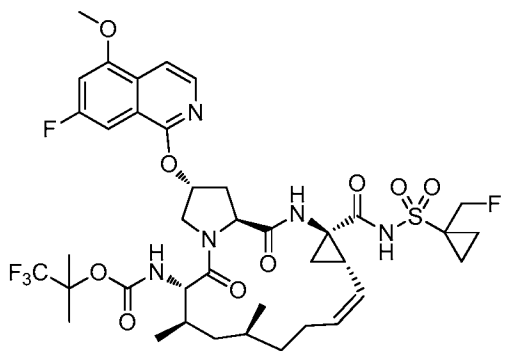
Compound 3174

Compounds 3173 and 3174 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

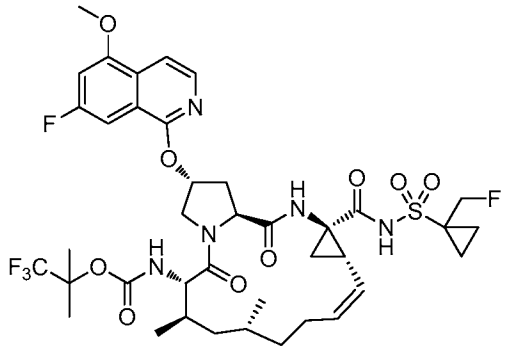
Compound 3173: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 804.4 (M^++1).

Compound 3174: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (br. s., 1H), 9.01 (br. s., 1H), 8.02 (d, *J*=6.1 Hz, 1H), 7.51 (d, *J*=5.8 Hz, 1H), 7.32 - 7.26 (m, 1H), 7.24 - 7.14 (m, 2H), 5.81 (br. s., 1H), 5.59 - 5.46 (m, 1H), 5.07 - 4.95 (m, 1H), 4.91 - 4.71 (m, 1H), 4.67 - 4.40 (m, 3H), 4.01 (s, 3H), 3.91 - 3.88 (m, *J*=8.5 Hz, 1H), 3.68 (dd, *J*=10.4, 8.2 Hz, 1H), 2.73 - 2.56 (m, 2H), 2.36 - 2.23 (m, 2H), 1.92 - 1.64 (m, 3H), 1.61 - 1.04 (m, 18H), 0.93 (d, *J*=6.7 Hz, 3H), 0.89 (d, *J*=6.4 Hz, 3H), 0.73 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 804.4 (M^++1).

Preparation of Compound 3175 and Compound 3176



Compound 3175



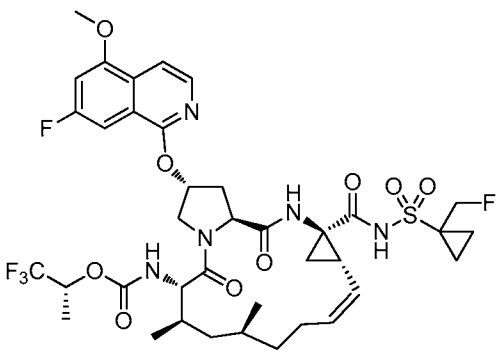
Compound 3176

Compounds 3175 and 3176 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

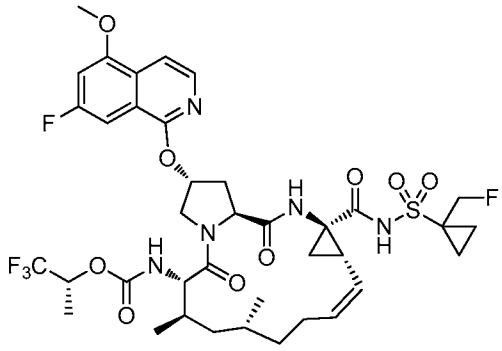
Compound 3175: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 858.4 (M^++1).

Compound 3176: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (s, 1H), 9.03 (br. s., 1H), 8.03 (d, *J*=5.8 Hz, 1H), 7.85 (d, *J*=7.0 Hz, 1H), 7.52 (d, *J*=5.8 Hz, 1H), 7.29 (dd, *J*=9.2, 1.8 Hz, 1H), 7.23 (dd, *J*=11.3, 2.1 Hz, 1H), 5.81 (br. s., 1H), 5.57 - 5.44 (m, 1H), 5.01 (t, *J*=9.6 Hz, 1H), 4.93 - 4.72 (m, 1H), 4.64 - 4.45 (m, 3H), 4.01 (s, 3H), 3.95 - 3.87 (m, 1H), 3.69 (dd, *J*=10.5, 8.1 Hz, 1H), 2.71 - 2.59 (m, 2H), 2.40 - 2.25 (m, 2H), 1.92 - 1.78 (m, 2H), 1.75 - 1.66 (m, 1H), 1.60 - 1.08 (m, 15H), 0.94 (d, *J*=6.7 Hz, 3H), 0.90 (d, *J*=6.4 Hz, 3H), 0.75 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 858.4 (M^++1).

Preparation of Compound 3177 and Compound 3178



Compound 3177



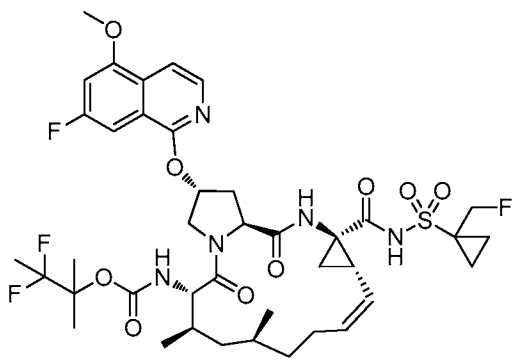
Compound 3178

Compounds 3177 and 3178 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

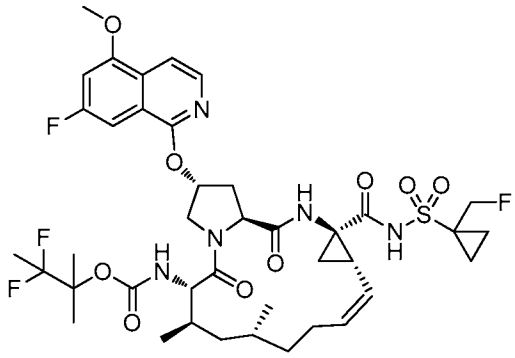
Compound 3177: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 858.4 (M^++1).

Compound 3178: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.25 (br. s., 1H), 8.99 (br. s., 1H), 8.13 (d, *J*=7.6 Hz, 1H), 8.01 (d, *J*=6.1 Hz, 1H), 7.52 (d, *J*=6.1 Hz, 1H), 7.37 (dd, *J*=9.6, 2.0 Hz, 1H), 7.22 (dd, *J*=11.1, 2.3 Hz, 1H), 5.80 (br. s., 1H), 5.57 - 5.47 (m, 1H), 5.07 - 4.97 (m, 1H), 4.91 - 4.72 (m, 2H), 4.64 - 4.40 (m, 3H), 4.01 (s, 3H), 3.95 - 3.88 (m, 1H), 3.79 (dd, *J*=10.7, 7.9 Hz, 1H), 2.63 (d, *J*=8.9 Hz, 2H), 2.34 - 2.24 (m, 2H), 1.95 - 1.79 (m, 2H), 1.75 - 1.65 (m, 1H), 1.59 - 1.10 (m, 12H), 0.93 (t, *J*=7.5 Hz, 6H), 0.77 (t, *J*=11.6 Hz, 1H); MS: MS *m/z* 858.4 (M^++1).

Preparation of Compound 3179 and Compound 3180



Compound 3179



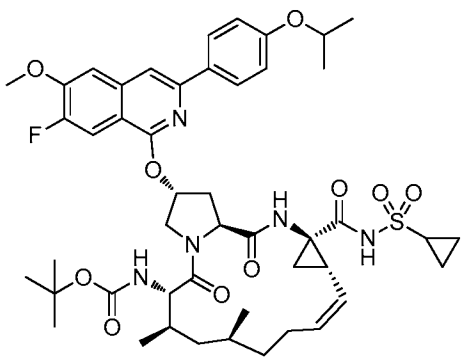
Compound 3180

Compounds 3179 and 3180 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

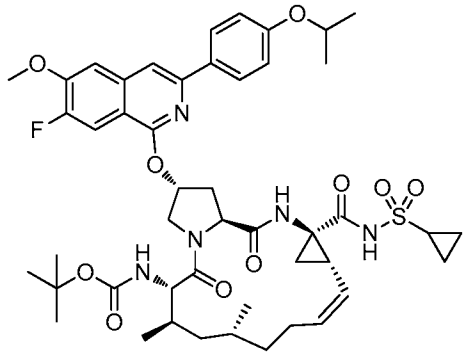
Compound 3179: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 854.4 (M^++1).

Compound 3180: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-5-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.96 (d, *J*=6.1 Hz, 1H), 7.57 (d, *J*=6.1 Hz, 1H), 7.34 (dd, *J*=9.2, 2.1 Hz, 1H), 7.02 (dd, *J*=11.0, 2.1 Hz, 1H), 5.88 (t, *J*=3.4 Hz, 1H), 5.56 (td, *J*=10.2, 5.8 Hz, 1H), 5.14 (t, *J*=9.8 Hz, 1H), 4.88 - 4.74 (m, 1H), 4.71 (d, *J*=11.9 Hz, 1H), 4.66 - 4.51 (m, 2H), 4.04 - 3.99 (m, 4H), 3.82 (d, *J*=10.7 Hz, 1H), 2.72 (dd, *J*=14.0, 7.3 Hz, 1H), 2.63 (q, *J*=9.2 Hz, 1H), 2.45 (ddd, *J*=14.0, 10.1, 4.0 Hz, 1H), 2.41 - 2.34 (m, 1H), 1.98 - 1.77 (m, 4H), 1.72 - 1.40 (m, 9H), 1.33 - 1.10 (m, 6H), 1.03 - 0.96 (m, 8H), 0.81 (t, *J*=12.3 Hz, 1H); MS: MS *m/z* 854.4 (M^++1).

Preparation of Compound 3181 and Compound 3181



Compound 3181



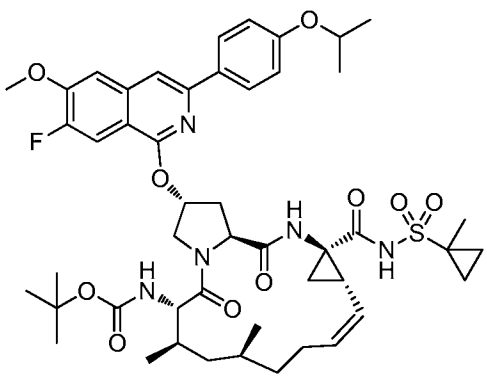
Compound 3182

Compounds 3181 and 3182 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

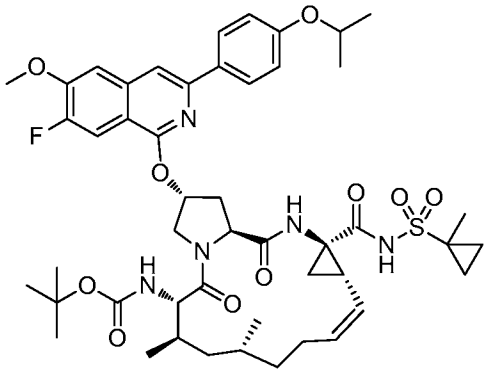
Compound 3181: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 906.8 (M^++1).

Compound 3182: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.23 (br. s., 1H), 8.93 (br. s., 1H), 8.10 (d, *J*=8.5 Hz, 2H), 7.85 (s, 1H), 7.71 (d, *J*=11.3 Hz, 1H), 7.55 (d, *J*=8.2 Hz, 1H), 7.22 (d, *J*=7.6 Hz, 1H), 7.06 (d, *J*=8.9 Hz, 2H), 5.96 (br. s., 1H), 5.59 - 5.47 (m, 1H), 5.07 (t, *J*=8.5 Hz, 1H), 4.72 (spt, *J*=6.1 Hz, 1H), 4.60 (d, *J*=11.3 Hz, 1H), 4.51 - 4.43 (m, 1H), 4.00 (s, 3H), 3.94 (dd, *J*=11.0, 3.1 Hz, 1H), 3.72 (dd, *J*=10.4, 8.5 Hz, 1H), 2.97 - 2.87 (m, 1H), 2.77 - 2.64 (m, 2H), 2.42 - 2.25 (m, 2H), 1.98 - 1.68 (m, 3H), 1.66 - 1.51 (m, 2H), 1.49 - 0.84 (m, 28H), 0.75 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 906.8 (M^++1).

Preparation of Compound 3183 and Compound 3184



Compound 3183



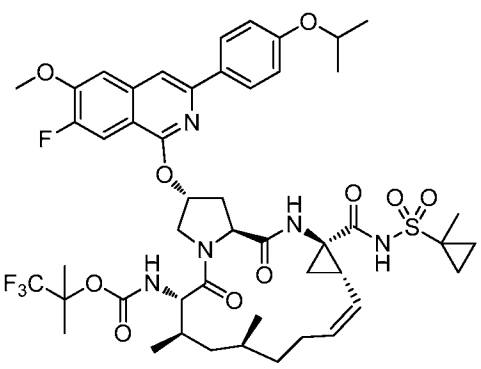
Compound 3184

Compounds 3183 and 3184 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

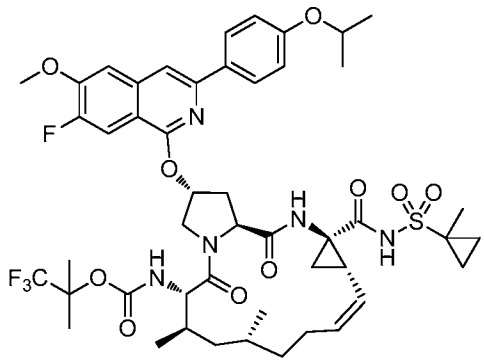
Compound 3183: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 920.8 (M^++1).

Compound 3184: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.07 (br. s., 1H), 9.06 (br. s., 1H), 8.09 (d, *J*=8.9 Hz, 2H), 7.85 (s, 1H), 7.71 (d, *J*=11.3 Hz, 1H), 7.55 (d, *J*=8.2 Hz, 1H), 7.22 (d, *J*=7.6 Hz, 1H), 7.06 (d, *J*=8.9 Hz, 2H), 5.97 (br. s., 1H), 5.57 - 5.47 (m, 1H), 5.06 - 4.94 (m, 1H), 4.72 (spt, *J*=6.0 Hz, 1H), 4.60 (d, *J*=13.4 Hz, 1H), 4.55 - 4.46 (m, 1H), 4.00 (s, 3H), 3.96 (dd, *J*=11.3, 3.1 Hz, 1H), 3.72 (dd, *J*=10.5, 8.4 Hz, 1H), 2.79 - 2.62 (m, 2H), 2.43 - 2.27 (m, 2H), 1.97 - 0.84 (m, 36H), 0.75 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 920.8 (M^++1).

Preparation of Compound 3185 and Compound 3186



Compound 3185



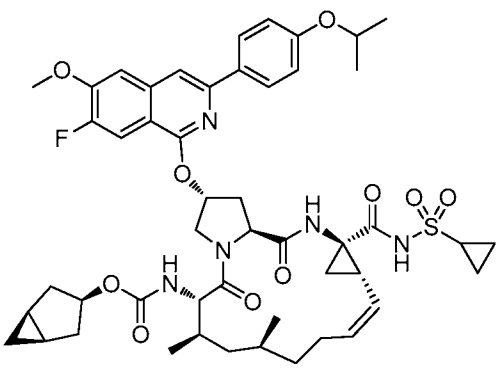
Compound 3186

Compounds 3185 and 3186 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

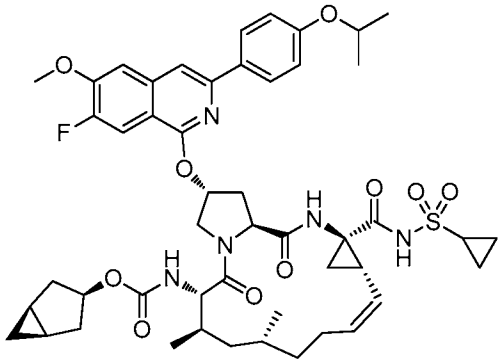
Compound 3185: MS: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS *m/z* 974.7 (M^++1).

Compound 3186: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.09 (br. s., 1H), 8.09 (d, *J*=8.9 Hz, 2H), 7.86 (s, 1H), 7.71 (d, *J*=11.6 Hz, 1H), 7.56 (d, *J*=8.5 Hz, 1H), 7.07 (d, *J*=8.9 Hz, 2H), 5.98 (br. s., 1H), 5.54 (d, *J*=5.5 Hz, 1H), 5.00 (t, *J*=9.6 Hz, 1H), 4.73 (spt, *J*=6.1 Hz, 1H), 4.59 - 4.48 (m, 2H), 4.01 (s, 3H), 3.97 (dd, *J*=11.4, 3.2 Hz, 1H), 3.74 (dd, *J*=10.7, 7.9 Hz, 1H), 2.74 - 2.63 (m, 2H), 2.41 - 2.27 (m, 2H), 1.96 - 1.79 (m, 2H), 1.78 - 1.68 (m, 1H), 1.65 - 1.58 (m, 1H), 1.57 - 1.51 (m, 1H), 1.50 - 1.09 (m, 28H), 0.99 - 0.85 (m, 8H), 0.78 (t, *J*=12.7 Hz, 1H); MS: MS *m/z* 974.7 (M^++1).

Preparation of Compound 3187 and Compound 3188



Compound 3187



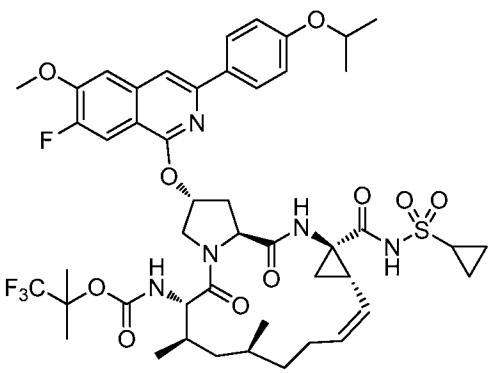
Compound 3188

Compounds 3187 and 3188 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

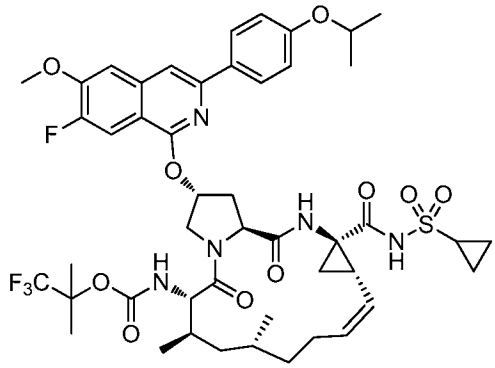
Compound 3187: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 930.7 (M^++1).

Compound 3188: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.87 (s, 1H), 8.10 (d, *J*=8.5 Hz, 2H), 7.86 (s, 1H), 7.81 (d, *J*=11.6 Hz, 1H), 7.56 (d, *J*=8.5 Hz, 1H), 7.47 (d, *J*=8.2 Hz, 1H), 7.07 (d, *J*=8.9 Hz, 2H), 5.94 (br. s., 1H), 5.58 - 5.48 (m, 1H), 5.08 (t, *J*=10.1 Hz, 1H), 4.84 (t, *J*=6.7 Hz, 1H), 4.72 (spt, *J*=6.0 Hz, 1H), 4.55 (d, *J*=11.3 Hz, 1H), 4.45 (dd, *J*=10.1, 7.0 Hz, 1H), 4.01 (s, 3H), 3.94 (dd, *J*=11.1, 3.2 Hz, 1H), 3.77 (dd, *J*=10.7, 8.2 Hz, 1H), 2.97 - 2.88 (m, 1H), 2.80 - 2.64 (m, 2H), 2.42 - 2.22 (m, 2H), 2.06 - 1.79 (m, 4H), 1.75 - 0.86 (m, 26H), 0.76 (t, *J*=12.4 Hz, 1H), 0.47 - 0.34 (m, 2H); MS: MS *m/z* 930.7 (M^++1).

Preparation of Compound 3189 and Compound 3190



Compound 3189



Compound 3190

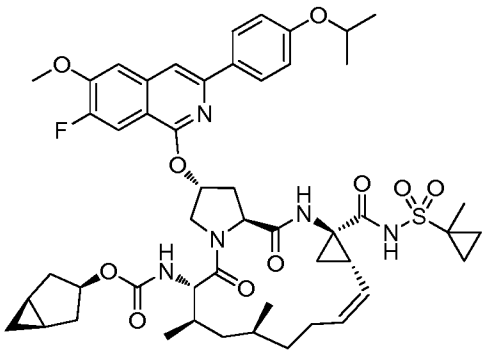
Compounds 3189 and 3190 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 3189: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 960.8 (M^++1).

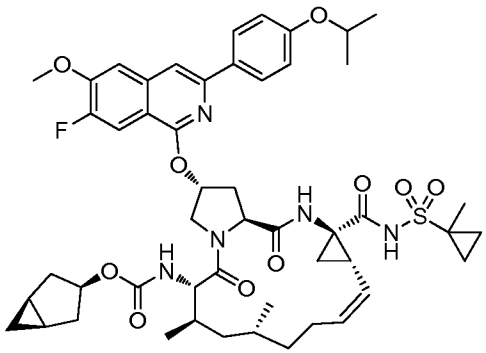
Compound 3190: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.95 (s, 1H), 8.10 (d, *J*=8.9 Hz, 2H), 7.87 (s, 2H), 7.71 (d, *J*=11.6 Hz, 1H), 7.57 (d, *J*=8.2 Hz, 1H), 7.07 (d, *J*=8.9 Hz, 2H), 5.96 (br. s., 1H), 5.59 - 5.48 (m, 1H), 5.08 (t, *J*=9.9 Hz, 1H), 4.73 (spt, *J*=6.0 Hz, 1H), 4.59 - 4.44 (m, 2H), 4.01 (s, 3H), 3.95 (dd, *J*=11.4, 3.2 Hz, 1H), 3.74 (dd, *J*=10.7, 7.6 Hz, 1H), 2.98 - 2.88 (m, 1H), 2.80 - 2.63 (m, 2H), 2.44 - 2.24 (m, 2H), 1.99 - 1.81 (m, 2H), 1.79 - 1.71 (m, 1H), 1.65 - 1.53 (m, 2H), 1.51 - 0.97 (m, 19H), 0.95 (d, *J*=7.0

Hz, 3H), 0.91 (d, *J*=6.1 Hz, 3H), 0.77 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 960.8 (M^++1).

Preparation of Compound 3191 and Compound 3192



Compound 3191



Compound 3192

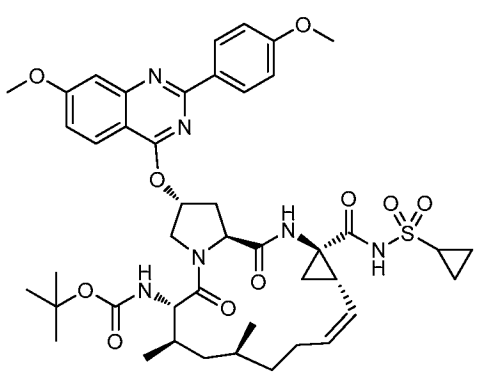
Compounds 3191 and 3192 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 3191: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 944.8 (M^++1).

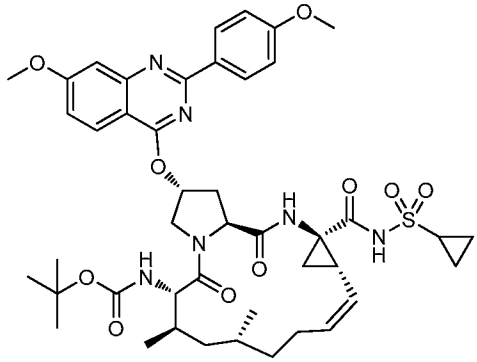
Compound 3192: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.00 (s, 1H), 8.09 (d, *J*=8.9 Hz, 2H), 7.86 (s, 1H), 7.80 (d, *J*=11.6 Hz, 1H), 7.56 (d, *J*=8.2 Hz, 1H), 7.47 (d, *J*=7.9 Hz, 1H), 7.07 (d, *J*=8.9 Hz, 2H), 5.96 (br. s., 1H), 5.58 - 5.48 (m, 1H), 5.00 (t, *J*=9.8 Hz, 1H), 4.82 (t, *J*=6.7 Hz, 1H), 4.72 (spt, *J*=6.1 Hz, 1H), 4.60 - 4.44 (m, 2H), 4.01 (s, 3H), 3.96 (dd, *J*=11.3, 3.4 Hz, 1H), 3.77 (dd, *J*=10.5, 8.4 Hz, 1H), 2.78 - 2.67 (m, 1H), 2.42 - 2.25 (m, 2H), 2.04 - 1.80 (m,

4H), 1.75 - 1.11 (m, 22H), 1.01 - 0.85 (m, 8H), 0.77 (t, *J*=12.1 Hz, 1H), 0.46 - 0.33 (m, 2H); MS: MS *m/z* 944.7 (M^++1).

Preparation of Compound 5001 and Compound 5002



Compound 5001



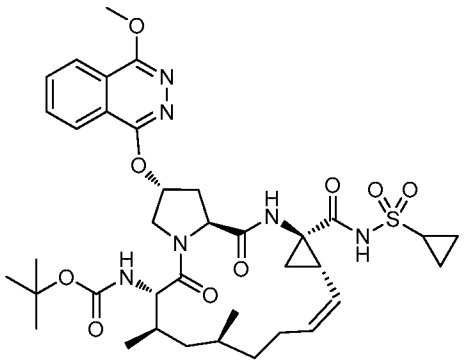
Compound 5002

Compound 5001 and Compound 5002 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

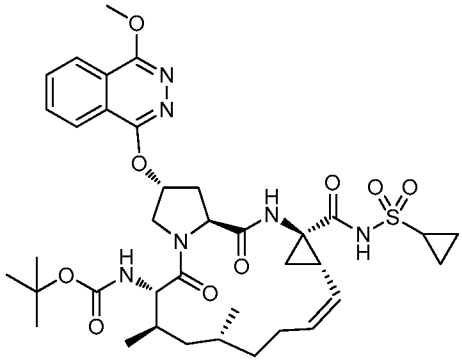
Compound 5001: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-methoxy-2-(4-methoxyphenyl)quinazolin-4-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 861.4 (M^++1).

Compound 5002: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-methoxy-2-(4-methoxyphenyl)quinazolin-4-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm11.22 (br. s., 1H), 8.95 (br. s., 1H), 8.50 (d, *J*=8.9 Hz, 2H), 7.98 (d, *J*=9.2 Hz, 1H), 7.32 (d, *J*=2.4 Hz, 1H), 7.20 (d, *J*=7.6 Hz, 1H), 7.15 - 7.05 (m, 3H), 6.04 (br. s., 1H), 5.51 (br. s., 1H), 5.09 (br. s., 1H), 4.67 (d, *J*=10.4 Hz, 1H), 4.52 - 4.43 (m, 1H), 4.01 - 3.93 (m, 4H), 3.87 (s, 3H), 3.74 - 3.66 (m, 1H), 2.90 (s, 1H), 2.70 - 2.65 (br. s., 1H), 2.46 - 2.36 (m, 1H), 2.29 (d, *J*=12.5 Hz, 1H), 1.92 (s, 1H), 1.82 (d, *J*=5.5 Hz, 1H), 1.72 (br. s., 1H), 1.59 (br. s., 2H), 1.42 - 1.32 (m, 4H), 1.14 - 0.73 (m, 20H); MS: MS *m/z* 861.4 (M^++1).

Preparation of Compound 5003 and Compound 5004



Compound 5003



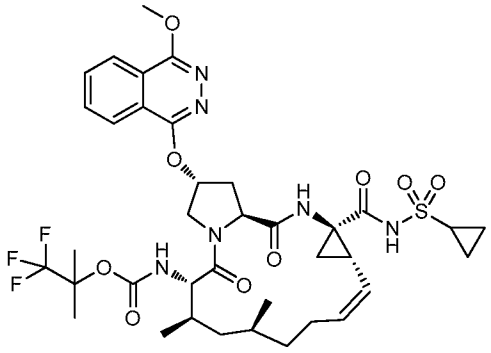
Compound 5004

Compound 5003 and Compound 5004 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

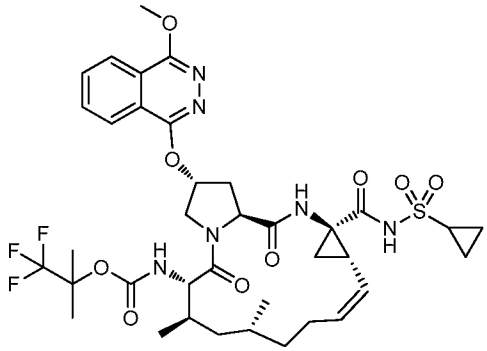
Compound 5003: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-methoxyphthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 755.34 (M^++1).

Compound 5004: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-methoxyphthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.21 (br. s., 1H), 9.02 (br. s., 1H), 8.12 (d, *J*=7.9 Hz, 1H), 8.06 (d, *J*=7.9 Hz, 1H), 8.02 - 7.87 (m, 2H), 7.16 (d, *J*=7.6 Hz, 1H), 5.83 (br. s., 1H), 5.53 (br. s., 1H), 5.04 (br. s., 1H), 4.69 (d, *J*=11.0 Hz, 1H), 4.57 - 4.43 (m, 1H), 4.12 (s, 3H), 3.89 (dd, *J*=11.6, 3.1 Hz, 1H), 3.67 (dd, *J*=10.7, 8.2 Hz, 1H), 2.91 (d, *J*=7.9 Hz, 1H), 2.68 (d, *J*=6.4 Hz, 2H), 2.39 - 2.25 (m, 2H), 1.96 - 1.86 (m, 1H), 1.85 - 1.76 (m, 1H), 1.71 (br. s., 1H), 1.62 (br. s., 1H), 1.55 (br. s., 1H), 1.42 (br. s., 1H), 1.37 (br. s., 1H), 1.13 - 0.73 (m, 21H); MS: MS *m/z* 755.34 (M^++1).

Preparation of Compound 5005 and Compound 5006



Compound 5005



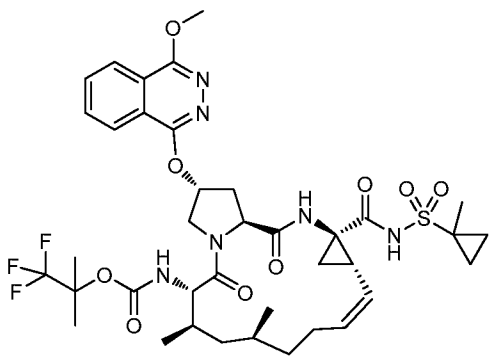
Compound 5006

Compound 5005 and Compound 5006 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

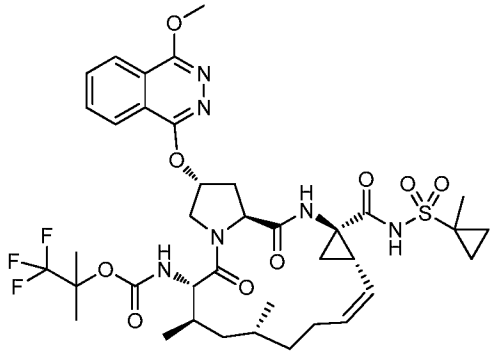
Compound 5005: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-methoxyphthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 809.3 (M^++1).

Compound 5006: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-methoxyphthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.21 (br. s., 1H), 9.05 (br. s., 1H), 8.13 (d, *J*=7.6 Hz, 1H), 8.07 - 7.93 (m, 3H), 7.81 (d, *J*=7.6 Hz, 1H), 5.84 (br. s., 1H), 5.54 (br. s., 1H), 5.05 (br. s., 1H), 4.62 (d, *J*=11.0 Hz, 1H), 4.56 - 4.47 (m, 1H), 4.12 (s, 3H), 3.95 - 3.86 (m, 1H), 3.67 (dd, *J*=10.7, 7.9 Hz, 1H), 2.99 - 2.88 (m, 1H), 2.66 (d, *J*=10.4 Hz, 2H), 2.40 - 2.23 (m, 2H), 1.95 - 1.78 (m, 2H), 1.71 (br. s., 1H), 1.62 (br. s., 1H), 1.57 (br. s., 1H), 1.48 - 1.32 (m, 2H), 1.27 (s, 3H), 1.14 (br. s., 3H), 1.05 - 0.85 (m, 11H), 0.75 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 809.3 (M^++1).

Preparation of Compound 5007 and Compound 5008



Compound 5007



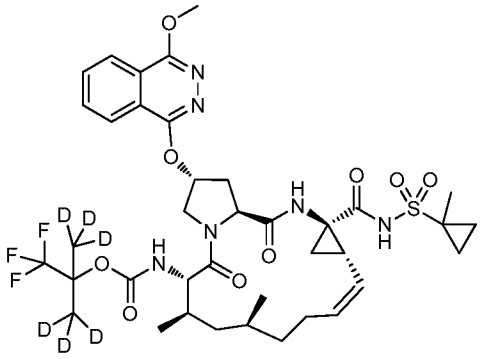
Compound 5008

Compound 5007 and Compound 5008 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

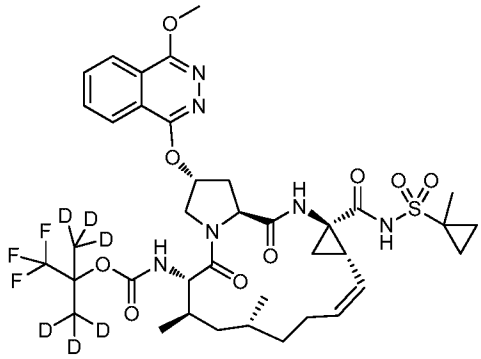
Compound 5007: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-methoxyphthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 823.3 (M^++1).

Compound 5008: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-methoxyphthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.06 (br. s., 1H), 9.17 (br. s., 1H), 8.14 (d, *J*=7.6 Hz, 1H), 8.04 (d, *J*=8.2 Hz, 1H), 8.02 - 7.94 (m, 2H), 7.82 (d, *J*=7.6 Hz, 1H), 5.85 (br. s., 1H), 5.52 (br. s., 1H), 4.99 (br. s., 1H), 4.63 (d, *J*=11.0 Hz, 1H), 4.55 (t, *J*=8.1 Hz, 1H), 4.12 (s, 3H), 3.96 - 3.89 (m, 1H), 3.67 (dd, *J*=10.5, 7.8 Hz, 1H), 2.67 (br. s., 2H), 2.35 (ddd, *J*=14.0, 10.4, 4.0 Hz, 2H), 1.92 - 1.79 (m, 2H), 1.70 (br. s., 1H), 1.61 (br. s., 1H), 1.50 (d, *J*=14.3 Hz, 1H), 1.41- 1.17 (m, 11H), 0.98 - 0.76 (m, 12H); MS: MS *m/z* 823.3 (M^++1).

Preparation of Compound 5009 and Compound 5010



Compound 5009



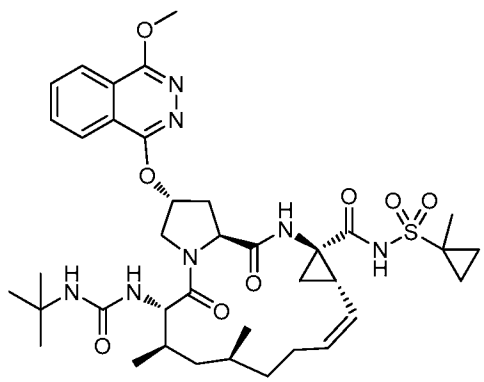
Compound 5010

Compound 5009 and Compound 5010 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

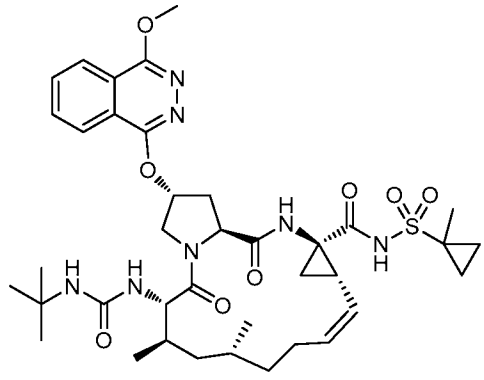
Compound 5009: MS: MS *m/z* 829.6 (M^++1).

Compound 5010: ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.06 (br. s., 1H), 9.18 (br. s., 1H), 8.14 (d, *J*=7.3 Hz, 1H), 8.04 (d, *J*=8.5 Hz, 1H), 8.02 - 7.94 (m, 2H), 7.82 (d, *J*=7.3 Hz, 1H), 5.85 (br. s., 1H), 5.52 (br. s., 1H), 4.99 (br. s., 1H), 4.63 (d, *J*=11.6 Hz, 1H), 4.55 (t, *J*=8.2 Hz, 1H), 3.95 - 3.88 (m, 1H), 3.67 (dd, *J*=10.7, 7.6 Hz, 1H), 2.67 (br. s., 2H), 2.35 (ddd, *J*=14.0, 10.2, 4.1 Hz, 2H), 1.96 - 1.79 (m, 2H), 1.70 (br. s., 1H), 1.62 (br. s., 1H), 1.52 (br. s., 1H), 1.41 (s, 5H), 1.34 (d, *J*=12.2 Hz, 2H), 1.31 - 1.21 (m, 1H), 1.16 (br. s., 2H), 0.98 - 0.83 (m, 8H), 0.76 (t, *J*=12.2 Hz, 2H); MS: MS *m/z* 829.6 (M^++1).

Preparation of Compound 5011 and Compound 5012



Compound 5011



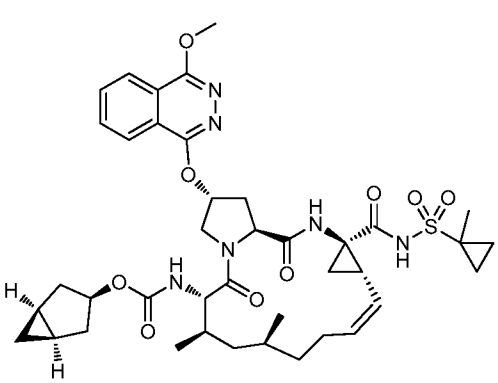
Compound 5012

Compound 5011 and Compound 5012 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

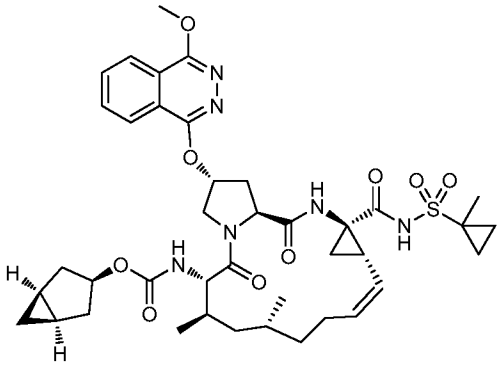
Compound 5011: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-2-((4-methoxyphthalazin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 768.4 (M^++1).

Compound 5012: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-2-((4-methoxyphthalazin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.08 (br. s., 1H), 9.11 (br. s., 1H), 8.15 - 8.04 (m, 2H), 7.98 (t, *J*=7.2 Hz, 1H), 7.94 - 7.88 (m, 1H), 5.92 (d, *J*=8.5 Hz, 1H), 5.84 (br. s., 1H), 5.52 (s, 2H), 4.99 (br. s., 1H), 4.67 (br. s., 1H), 4.46 (br. s., 1H), 4.12 (s, 3H), 3.97 - 3.88 (m, 1H), 3.80 (t, *J*=9.5 Hz, 1H), 2.65 (br. s., 1H), 2.41 - 2.26 (m, 2H), 1.94 - 1.82 (m, 2H), 1.72 (br. s., 1H), 1.69 - 1.50 (m, 3H), 1.40 (br. s., 5H), 1.35 (br. s., 1H), 1.27 (br. s., 1H), 1.24 - 1.08 (m, 1H), 0.98 - 0.85 (m, 16H), 0.81 (br. s., 1H), 0.74 (t, *J*=11.7 Hz, 1H); MS: MS *m/z* 768.4 (M^++1).

Preparation of Compound 5013 and Compound 5014



Compound 5013



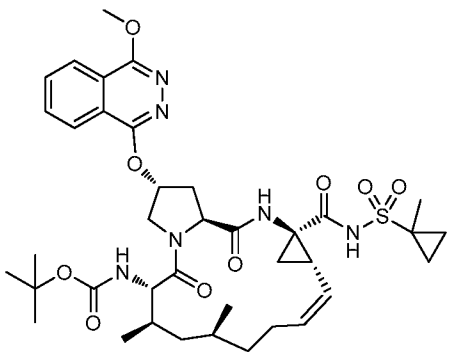
Compound 5014

Compound 5013 and Compound 5014 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

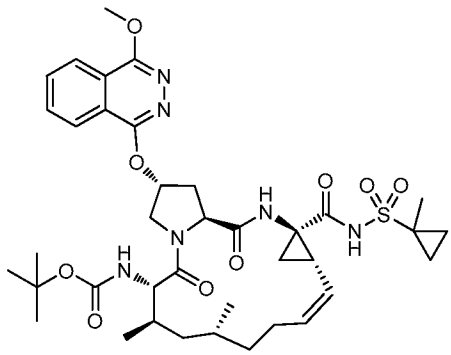
Compound 5013: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-methoxyphthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 793.6 (M^++1).

Compound 5014: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-methoxyphthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.06 (br. s., 1H), 9.10 (br. s., 1H), 8.14 (d, *J*=7.3 Hz, 1H), 8.08 - 7.92 (m, 3H), 7.38 (br. s., 1H), 5.86 (br. s., 1H), 5.52 (br. s., 1H), 4.99 (br. s., 1H), 4.51 (br. s., 2H), 4.43 (t, *J*=6.4 Hz, 1H), 4.13 (s, 3H), 3.97 - 3.92 (m, 1H), 3.77 - 3.67 (m, 1H), 2.67 (d, *J*=15.0 Hz, 2H), 2.40 - 2.24 (m, 2H), 1.99 - 1.77 (m, 4H), 1.74 - 1.59 (m, 3H), 1.52 (d, *J*=14.3 Hz, 2H), 1.41 (br. s., 5H), 1.30 - 1.23 (m, 2H), 1.21 - 1.12 (m, 2H), 1.12 - 1.05 (m, 1H), 0.93 (d, *J*=7.0 Hz, 4H), 0.87 (d, *J*=6.4 Hz, 4H), 0.74 (br. s., 1H), 0.36 - 0.24 (m, 2H); MS: MS *m/z* 793.6 (M^++1).

Preparation of Compound 5015 and Compound 5016



Compound 5015



Compound 5016

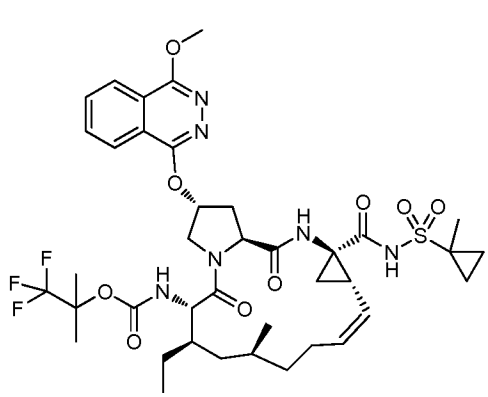
Compound 5015 and Compound 5016 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5015: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-methoxyphthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

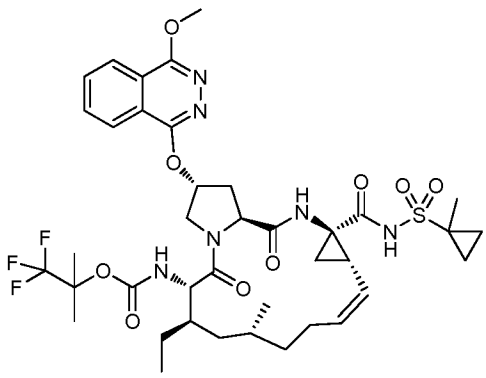
1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 769.4 (M^++1).

Compound 5016: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-methoxyphthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.07 (br. s., 1H), 9.12 (br. s., 1H), 8.12 (d, *J*=7.9 Hz, 1H), 8.06 (d, *J*=7.9 Hz, 1H), 8.01 - 7.96 (m, 1H), 7.95 - 7.90 (m, 1H), 7.17 (d, *J*=7.3 Hz, 1H), 5.83 (br. s., 1H), 5.51 (br. s., 1H), 5.00 (br. s., 1H), 4.68 (d, *J*=11.0 Hz, 1H), 4.51 (br. s., 1H), 4.12 (s, 3H), 3.93 - 3.88 (m, 1H), 3.67 (dd, *J*=10.4, 8.2 Hz, 1H), 2.65 (br. s., 2H), 2.40 - 2.27 (m, 2H), 1.94 - 1.85 (m, 1H), 1.80 (d, *J*=6.4 Hz, 1H), 1.70 (br. s., 1H), 1.60 (br. s., 1H), 1.50 (br. s., 1H), 1.41 (br. s., 5H), 1.35 - 1.15 (m, 3H), 1.03 (s, 9H), 0.97 - 0.81 (m, 8H), 0.73 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 769.4 (M^++1).

Preparation of Compound 5017 and Compound 5018



Compound 5017



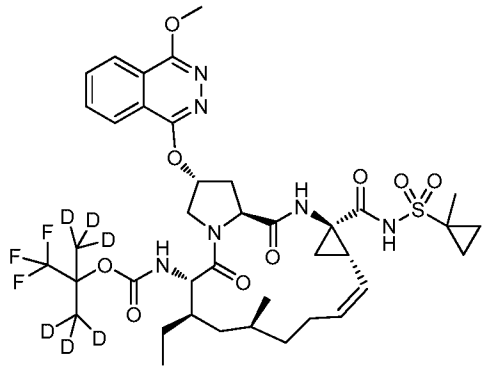
Compound 5018

Compound 5017 and Compound 5018 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

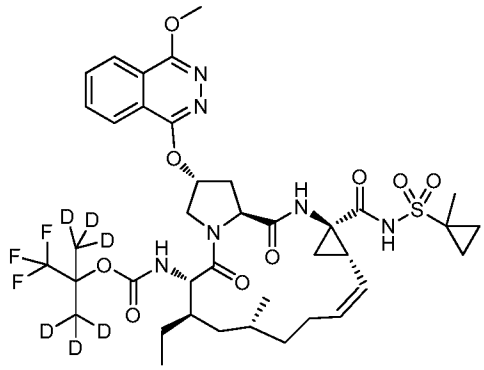
Compound 5017: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((4-methoxyphthalazin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 837.3 (M^++1).

Compound 5018: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((4-methoxyphthalazin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.06 (br. s., 1H), 9.17 (br. s., 1H), 8.14 (d, *J*=7.3 Hz, 1H), 8.06 - 7.94 (m, 3H), 7.87 (d, *J*=7.9 Hz, 1H), 5.87 (br. s., 1H), 5.53 (br. s., 1H), 4.98 (br. s., 1H), 4.63 (d, *J*=11.6 Hz, 1H), 4.60 - 4.48 (m, 1H), 4.13 (s, 3H), 3.99 - 3.90 (m, 1H), 3.86 (dd, *J*=10.7, 8.5 Hz, 1H), 2.72 - 2.61 (m, 2H), 2.41 - 2.25 (m, 2H), 2.01 - 1.83 (m, 2H), 1.63 (br. s., 1H), 1.58 - 1.40 (m, 8H), 1.36 (d, *J*=13.1 Hz, 2H), 1.29 (s, 4H), 1.18 (br. s., 1H), 1.02 (t, *J*=11.9 Hz, 1H), 0.96 - 0.86 (m, 8H), 0.73 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 837.3 (M^++1).

Preparation of Compound 5019 and Compound 5020



Compound 5019



Compound 5020

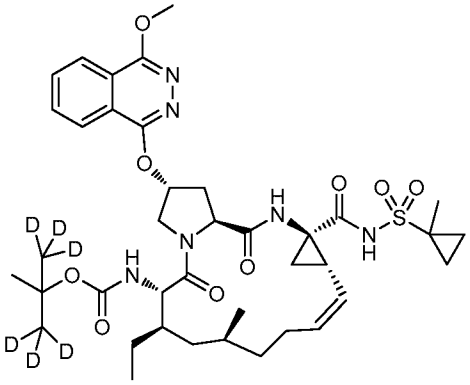
Compound 5019 and Compound 5020 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5019: MS: MS *m/z* 843.5 (M^++1).

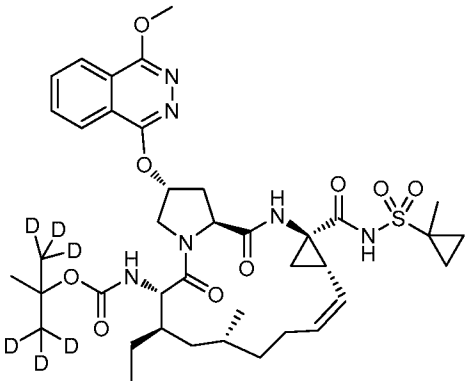
Compound 5020: ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.06 (br. s., 1H), 9.17 (br. s., 1H), 8.14 (d, *J*=7.6 Hz, 1H), 8.06 - 7.93 (m, 3H), 7.86 (d, *J*=8.2 Hz, 1H), 5.87 (br. s., 1H), 5.53 (br. s., 1H), 4.98 (br. s., 1H), 4.63 (d, *J*=11.9 Hz, 1H), 4.55 (d, *J*=7.3 Hz, 1H), 4.17 - 4.07 (m, 3H), 3.98 - 3.91 (m, 1H), 3.90 - 3.81 (m, 1H), 2.67 (d, *J*=18.3 Hz, 2H), 2.41 - 2.24 (m, 2H), 2.00 - 1.85 (m, 2H), 1.62 (br. s., 1H), 1.51 (br. s., 2H), 1.46 (br. s., 2H), 1.42 (br. s., 5H), 1.35 (br. s., 1H), 1.32 - 1.22 (m, 1H), 1.18 (br. s.,

1H), 1.08 - 0.98 (m, 1H), 0.93 (d, *J*=6.4 Hz, 5H), 0.73 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 843.5 (M^++1).

Preparation of Compound 5021 and Compound 5022



Compound 5021



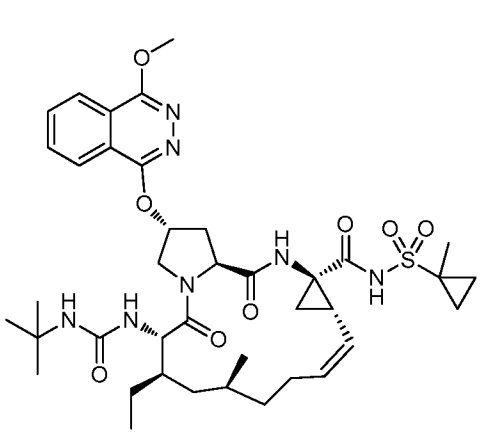
Compound 5022

Compound 5021 and Compound 5022 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

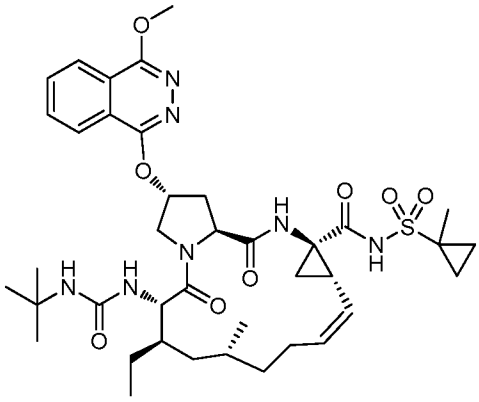
Compound 5021: MS: MS *m/z* 789.5 (M^++1).

Compound 5022: ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.07 (br. s., 1H), 9.14 (br. s., 1H), 8.12 (d, *J*=7.9 Hz, 1H), 8.04 (d, *J*=7.6 Hz, 1H), 8.01 - 7.90 (m, 2H), 7.18 (d, *J*=7.6 Hz, 1H), 5.85 (br. s., 1H), 5.52 (br. s., 1H), 4.99 (br. s., 1H), 4.70 (d, *J*=10.7 Hz, 1H), 4.51 (d, *J*=6.7 Hz, 1H), 4.12 (s, 4H), 4.01 - 3.82 (m, 2H), 2.75 (s, 1H), 2.66 (br. s., 2H), 2.41 - 2.25 (m, 2H), 1.92 (s, 2H), 1.61 - 1.10 (m, 11H), 1.01 - 0.73 (m, 12H); MS: MS *m/z* 789.5 (M^++1).

Preparation of Compound 5023 and Compound 5024



Compound 5023



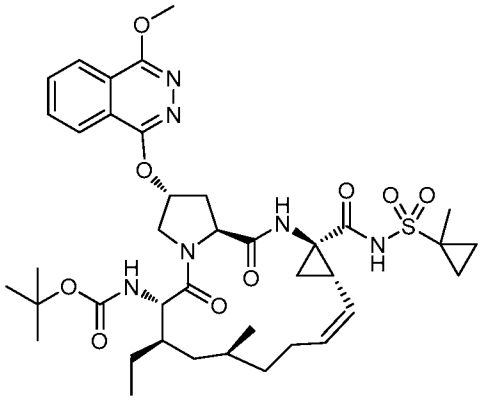
Compound 5024

Compound 5023 and Compound 5024 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

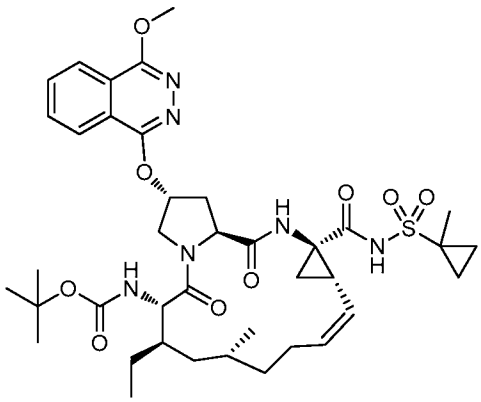
Compound 5023: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-7-ethyl-2-((4-methoxyphthalazin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 782.5 (M^++1).

Compound 5024: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-7-ethyl-2-((4-methoxyphthalazin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.07 (br. s., 1H), 9.10 (br. s., 1H), 8.12 (d, *J*=8.2 Hz, 1H), 8.05 (d, *J*=7.9 Hz, 1H), 8.01 - 7.96 (m, 1H), 7.94 - 7.87 (m, 1H), 5.93 (d, *J*=8.9 Hz, 1H), 5.85 (br. s., 1H), 5.52 (s, 2H), 4.99 (br. s., 1H), 4.70 (d, *J*=11.3 Hz, 1H), 4.48 (t, *J*=8.1 Hz, 1H), 4.12 (s, 3H), 4.01 (t, *J*=9.9 Hz, 1H), 3.96 - 3.90 (m, 1H), 2.68 (m, 2H), 2.40 - 2.28 (m, 2H), 1.96 - 1.86 (m, 1H), 1.74 (br. s., 1H), 1.60 (br. s., 1H), 1.55 - 1.18 (m, 13H), 1.06 - 0.86 (m, 14H), 0.78 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 782.5 (M^++1).

Preparation of Compound 5025 and Compound 5026



Compound 5025



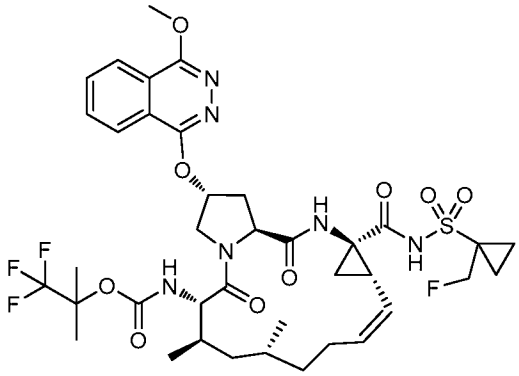
Compound 5026

Compound 5025 and Compound 5026 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5025: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((4-methoxyphthalazin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 783.5 (M^++1).

Compound 5026: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((4-methoxyphthalazin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.07 (br. s., 1H), 9.14 (br. s., 1H), 8.12 (d, *J*=7.9 Hz, 1H), 8.04 (d, *J*=7.6 Hz, 1H), 8.01 - 7.89 (m, 2H), 7.19 (d, *J*=7.9 Hz, 1H), 5.86 (br. s., 1H), 5.54 (br. s., 1H), 4.97 (br. s., 1H), 4.71 (d, *J*=11.9 Hz, 1H), 4.52 (d, *J*=7.3 Hz, 1H), 3.98 - 3.84 (m, 2H), 2.69 (br. s., 2H), 2.41 - 2.26 (m, 2H), 1.92 (s, 2H), 1.62 -1.15 (m, 14H), 1.02 - 0.86 (m, 17H), 0.73 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 783.5 (M^++1).

Preparation of Compound 5027

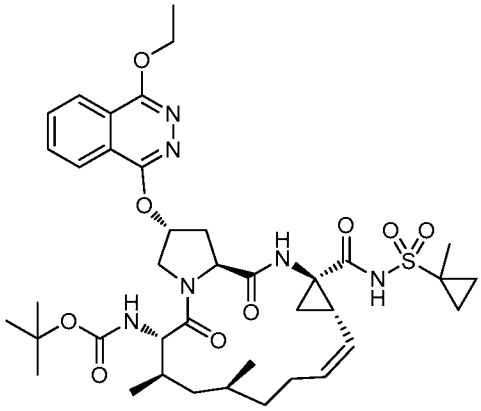


Compound 5027

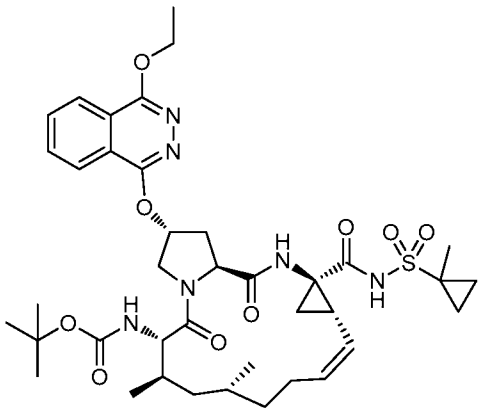
Compound 5027 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5027: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyphthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.30 (br. s., 1H), 9.10 (br. s., 1H), 8.14 (d, *J*=7.6 Hz, 1H), 8.06 - 7.93 (m, 3H), 7.83 (d, *J*=7.0 Hz, 1H), 5.84 (br. s., 1H), 5.52 (br. s., 1H), 4.99 (br. s., 1H), 4.88 – 4.76 (m, 1H), 4.67 - 4.52 (m, 3H), 4.16 - 4.09 (m, 3H), 3.94 - 3.88 (m, 1H), 3.68 (dd, *J*=10.7, 7.9 Hz, 1H), 3.18 (d, *J*=5.2 Hz, 1H), 2.65 (m, 2H), 2.40 - 2.27 (m, 2H), 1.90 - 1.77 (m, 2H), 1.70 (br. s., 1H), 1.54 (br. s., 3H), 1.41 (br. s., 1H), 1.37 (br. s., 1H), 1.31 - 1.21 (m, 5H), 1.16 (br. s., 1H), 0.99 (s, 3H), 0.94 (d, *J*=6.7 Hz, 3H), 0.89 (d, *J*=6.1 Hz, 3H), 0.80 - 0.72 (m, 1H); MS: MS *m/z* 841.6 (M^++1).

Preparation of Compound 5028 and Compound 5029



Compound 5028



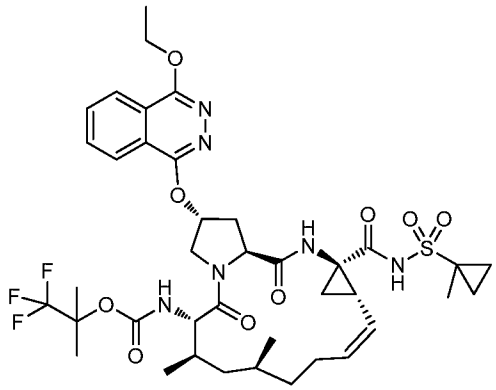
Compound 5029

Compound 5028 and Compound 5029 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

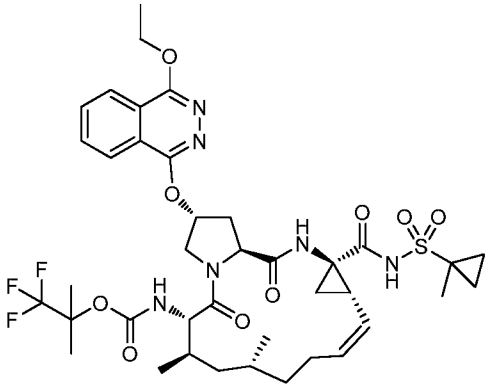
Compound 5028: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-ethoxyphthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 783.4 (M^++1).

Compound 5029: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-ethoxyphthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.07 (br. s., 1H), 9.14 (br. s., 1H), 8.12 (d, *J*=7.9 Hz, 1H), 8.05 (d, *J*=7.9 Hz, 1H), 8.00 - 7.95 (m, 1H), 7.95 - 7.89 (m, 1H), 7.17 (d, *J*=7.3 Hz, 1H), 5.83 (br. s., 1H), 5.52 (br. s., 1H), 4.97 (br. s., 1H), 4.74 - 4.65 (m, 1H), 4.61 - 4.47 (m, 3H), 3.94 - 3.87 (m, 1H), 3.68 (dd, *J*=10.7, 8.2 Hz, 1H), 2.67 (br. s., 2H), 2.40 - 2.21 (m, 2H), 1.94 - 1.86 (m, 1H), 1.81 (d, *J*=6.1 Hz, 1H), 1.69 (br. s., 1H), 1.62 (br. s., 1H), 1.52 - 1.09 (m, 12H), 1.03 (s, 9H), 0.93 - 0.88 (m, 8H), 0.74 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 783.4 (M^++1).

Preparation of Compound 5030 and Compound 5031



Compound 5030



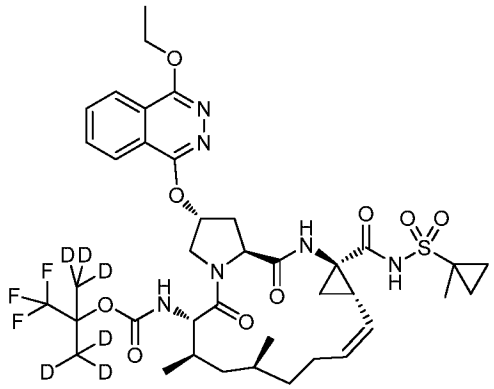
Compound 5031

Compound 5030 and Compound 5031 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

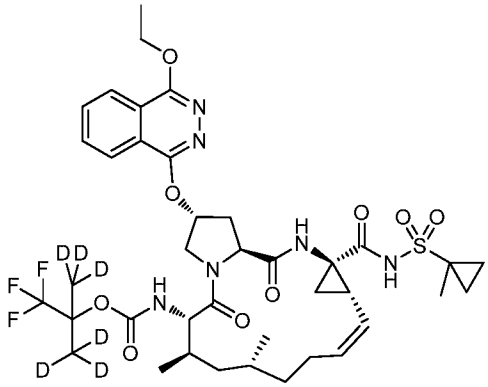
Compound 5030: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-ethoxyphthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 837.3 (M^++1).

Compound 5031: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-ethoxyphthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.17 (br. s., 1H), 8.13 (d, *J*=7.3 Hz, 1H), 8.06 - 7.92 (m, 3H), 7.82 (d, *J*=7.3 Hz, 1H), 5.84 (br. s., 1H), 5.53 (br. s., 1H), 4.99 (br. s., 1H), 4.67 - 4.60 (m, 1H), 4.60 - 4.50 (m, 3H), 3.96 - 3.86 (m, 1H), 3.68 (dd, *J*=10.8, 7.8 Hz, 1H), 2.67 (br. s., 2H), 2.35 (ddd, *J*=13.9, 10.4, 4.1 Hz, 2H), 1.93 - 1.79 (m, 2H), 1.70 (br. s., 1H), 1.61 (br. s., 1H), 1.52 (br. s., 1H), 1.47 (t, *J*=7.0 Hz, 4H), 1.41 (br. s., 4H), 1.35 - 1.15 (m, 7H), 0.96 (s, 3H), 0.93 (d, *J*=7.0 Hz, 3H), 0.89 (d, *J*=6.4 Hz, 4H), 0.76 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 837.3 (M^++1).

Preparation of Compound 5032 and Compound 5033



Compound 5032



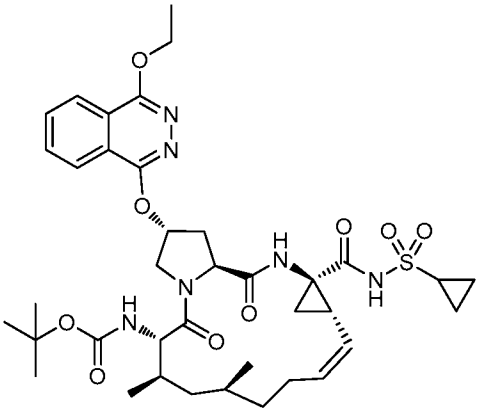
Compound 5033

Compound 5032 and Compound 5033 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

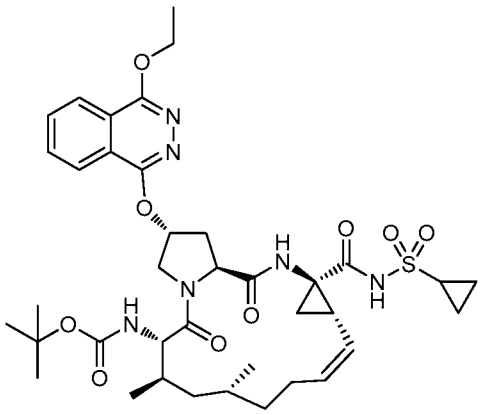
Compound 5032: MS: MS *m/z* 843.5 (M^++1).

Compound 5033: ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.06 (br. s., 1H), 9.17 (br. s., 1H), 8.13 (d, *J*=7.3 Hz, 1H), 8.06 - 7.92 (m, 3H), 7.82 (d, *J*=7.6 Hz, 1H), 5.84 (br. s., 1H), 5.54 (d, *J*=4.9 Hz, 1H), 4.98 (br. s., 1H), 4.64 (d, *J*=11.6 Hz, 1H), 4.59 - 4.47 (m, 3H), 3.97 - 3.89 (m, 1H), 3.68 (dd, *J*=10.7, 7.9 Hz, 1H), 2.68 (br. s., 2H), 2.41 - 2.28 (m, 2H), 1.94 - 1.79 (m, 2H), 1.74 - 1.67 (m, 1H), 1.63 (br. s., 1H), 1.53 (br. s., 1H), 1.47 (t, *J*=7.0 Hz, 4H), 1.42 (s, 4H), 1.37 - 11.14 (m, 4H), 0.93 (d, *J*=7.0 Hz, 3H), 0.89 (d, *J*=6.1 Hz, 4H), 0.76 (t, *J*=12.5 Hz, 1H)； MS: MS *m/z* 843.5 (M^++1).

Preparation of Compound 5034 and Compound 5035



Compound 5034



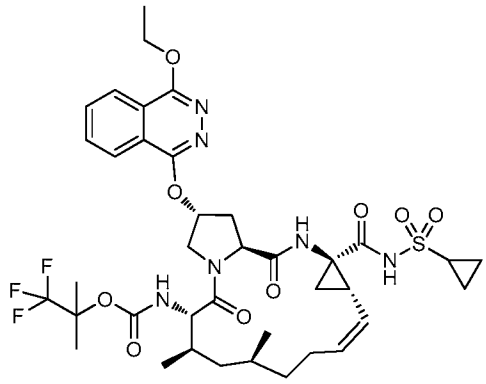
Compound 5035

Compound 5034 and Compound 5035 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

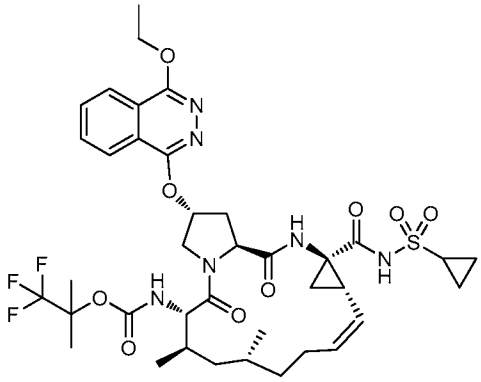
Compound 5034: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-ethoxyphthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 769.4 (M^++1).

Compound 5035: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-ethoxyphthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.21 (br. s., 1H), 9.02 (br. s., 1H), 8.12 (d, *J*=8.2 Hz, 1H), 8.05 (d, *J*=7.9 Hz, 1H), 7.98 (t, *J*=7.0 Hz, 1H), 7.95 - 7.89 (m, 1H), 7.16 (d, *J*=7.0 Hz, 1H), 5.82 (br. s., 1H), 5.53 (br. s., 1H), 5.05 (br. s., 1H), 4.69 (d, *J*=10.7 Hz, 1H), 4.61 - 4.52 (m, 2H), 4.51 - 4.42 (m, 1H), 3.95 - 3.86 (m, 1H), 3.68 (dd, *J*=10.4, 8.5 Hz, 1H), 2.91 (d, *J*=6.4 Hz, 1H), 2.68 (br. s., 2H), 2.42 - 2.23 (m, 2H), 1.96 - 1.86 (m, 1H), 1.85 - 1.76 (m, 1H), 1.72 (br. s., 1H), 1.61 (br. s., 1H), 1.55 (br. s., 1H), 1.49 - 1.39 (m, 4H), 1.36 (br. s., 1H), 1.13 (br. s., 2H), 1.05 (s, 10H), 1.00 (br. s., 1H), 0.94 (d, *J*=7.0 Hz, 4H), 0.88 (d, *J*=6.1 Hz, 3H), 0.73 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 769.4 (M^++1).

Preparation of Compound 5036 and Compound 5037



Compound 5036



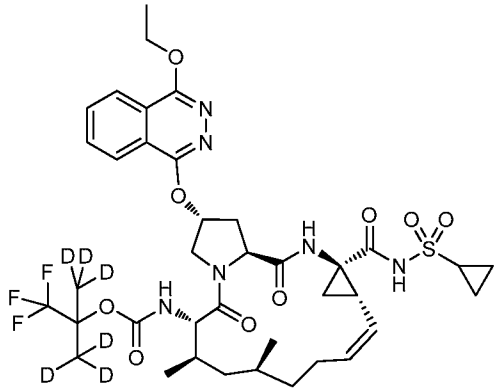
Compound 5037

Compound 5036 and Compound 5037 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

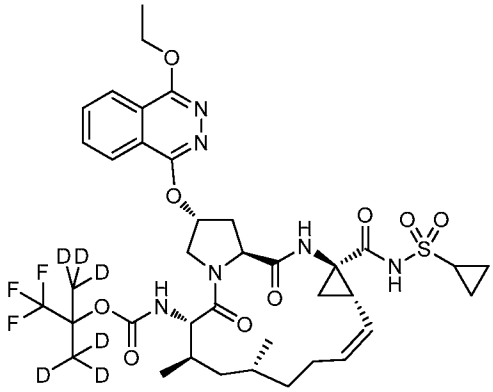
Compound 5036: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-ethoxyphthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 823.3 (M^++1).

Compound 5037: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-ethoxyphthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.20 (br. s., 1H), 9.04 (br. s., 1H), 8.17 - 8.10 (m, 1H), 8.06 - 7.90 (m, 3H), 7.81 (br. s., 1H), 5.82 (br. s., 1H), 5.52 (br. s., 1H), 5.06 (br. s., 1H), 4.66 - 4.45 (m, 4H), 3.93 - 3.81 (m, 1H), 3.74 - 3.60 (m, 1H), 2.91 (br. s., 1H), 2.67 (br. s., 2H), 2.34 (dd, *J*=14.5, 10.5 Hz, 2H), 1.95 - 1.82 (m, 2H), 1.71 (br. s., 1H), 1.59 (d, *J*=19.2 Hz, 2H), 1.46 - 1.36 (m, 4H), 1.28 (d, *J*=6.4 Hz, 3H), 1.20 - 1.13 (br. s., 3H), 1.03 - 0.85 (m, 12H), 0.74 (br. s., 1H); MS: MS *m/z* 823.3 (M^++1).

Preparation of Compound 5038 and Compound 5039



Compound 5038



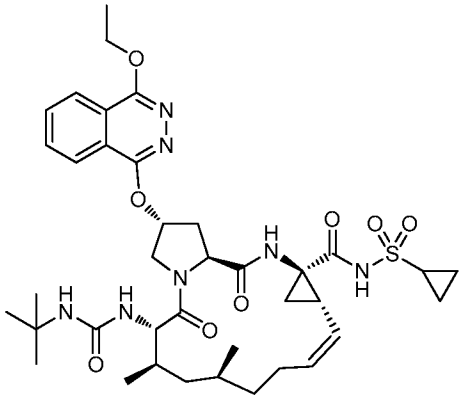
Compound 5039

Compound 5038 and Compound 5037 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

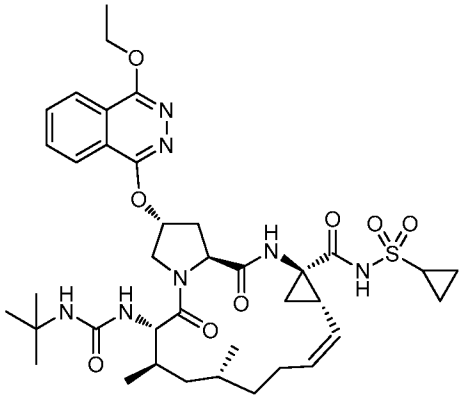
Compound 5038: MS: MS *m/z* 829.5 (M^++1).

Compound 5039: ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.20 (br. s., 1H), 9.04 (br. s., 1H), 8.13 (d, *J*=7.6 Hz, 1H), 8.07 - 7.92 (m, 3H), 7.81 (d, *J*=7.9 Hz, 1H), 5.83 (br. s., 1H), 5.53 (br. s., 1H), 5.06 (br. s., 1H), 4.67 - 4.44 (m, 4H), 3.96 - 3.84 (m, 1H), 3.68 (dd, *J*=10.8, 7.8 Hz, 1H), 2.91 (d, *J*=5.8 Hz, 1H), 2.67 (br. s., 2H), 2.40 - 2.23 (m, 2H), 1.94 - 1.78 (m, 2H), 1.71 (br. s., 1H), 1.61 (br. s., 1H), 1.56 (br. s., 1H), 1.47 (t, *J*=7.2 Hz, 3H), 1.42 (br. s., 1H), 1.35 (d, *J*=13.1 Hz, 1H), 1.18-0.99 (m, 5H), 0.94 (d, *J*=7.0 Hz, 3H), 0.89 (d, *J*=6.4 Hz, 3H), 0.75 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 829.5 (M^++1).

Preparation of Compound 5040 and Compound 5041



Compound 5040



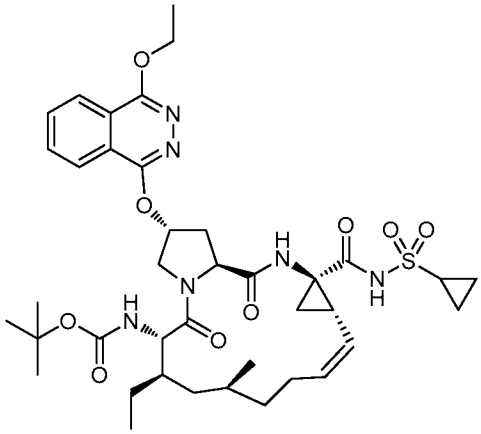
Compound 5041

Compound 5040 and Compound 5041 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

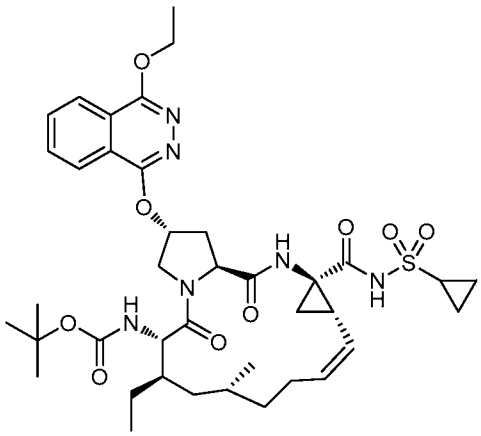
Compound 5040: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-N-(cyclopropylsulfonyl)-2-((4-ethoxyphthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 768.4 (M^++1).

Compound 5041: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-N-(cyclopropylsulfonyl)-2-((4-ethoxyphthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.21 (br. s., 1H), 8.98 (br. s., 1H), 8.11 (d, *J*=7.9 Hz, 1H), 8.06 (d, *J*=7.9 Hz, 1H), 8.00 - 7.93 (m, 1H), 7.92 - 7.85 (m, 1H), 5.92 (d, *J*=8.9 Hz, 1H), 5.83 (br. s., 1H), 5.52 (s, 2H), 5.05 (br. s., 1H), 4.68 (d, *J*=11.0 Hz, 1H), 4.56 (dtt, *J*=10.5, 7.0, 3.5 Hz, 2H), 4.49 - 4.39 (m, 1H), 3.94 - 3.87 (m, 1H), 3.83 - 3.75 (m, 1H), 2.91 (d, *J*=6.4 Hz, 1H), 2.69 (d, *J*=10.4 Hz, 2H), 2.39 - 2.23 (m, 2H), 1.96 - 1.85 (m, 1H), 1.71 (d, *J*=6.1 Hz, 1H), 1.63 (dd, *J*=18.6, 6.4 Hz, 2H), 1.54 (br. s., 1H), 1.47 (t, *J*=7.0 Hz, 4H), 1.44 - 1.32 (m, 2H), 1.14 (br. s., 2H), 1.08 (br. s., 2H), 0.98 - 0.93 (m, 12H), 0.90 (d, *J*=6.4 Hz, 3H), 0.74 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 768.4 (M^++1).

Preparation of Compound 5042 and Compound 5043



Compound 5042



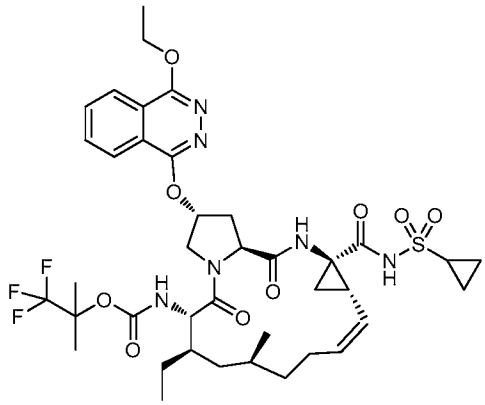
Compound 5043

Compound 5042 and Compound 5043 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

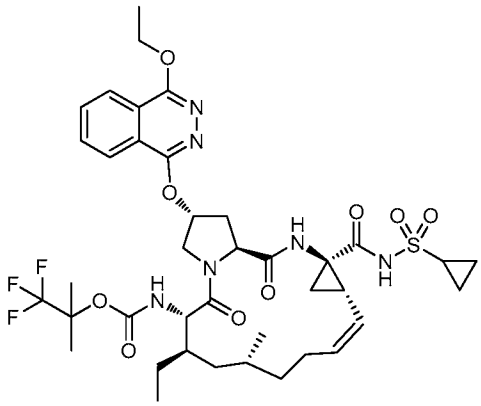
Compound 5042: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-ethoxyphthalazin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 783.4 (M^++1).

Compound 5043: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-ethoxyphthalazin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.21 (br. s., 1H), 9.01 (br. s., 1H), 8.12 (d, *J*=7.9 Hz, 1H), 8.03 (d, *J*=7.6 Hz, 1H), 8.00 - 7.96 (m, 1H), 7.93 (t, *J*=7.6 Hz, 1H), 7.18 (d, *J*=7.0 Hz, 1H), 5.83 (br. s., 1H), 5.52 (br. s., 1H), 5.05 (br. s., 1H), 4.69 (d, *J*=10.7 Hz, 1H), 4.61 - 4.44 (m, 3H), 3.94 - 3.81 (m, 2H), 2.91 (m, 1H), 2.71 - 2.60 (m, 2H), 2.40 - 2.22 (m, 2H), 1.92 (s, 2H), 1.61 - 1.30 (m, 11H), 1.25 - 0.87 (m, 17H), 0.77 - 0.73 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 783.4 (M^++1).

Preparation of Compound 5044 and Compound 5045



Compound 5044



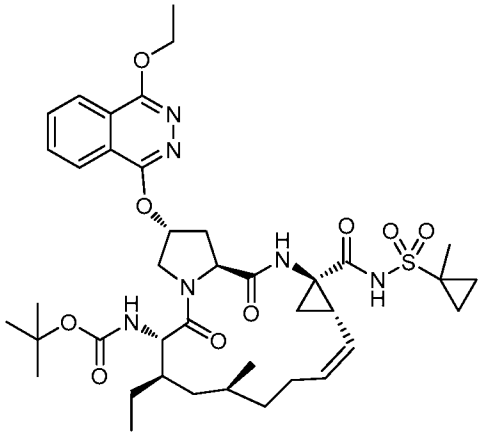
Compound 5045

Compound 5044 and Compound 5045 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

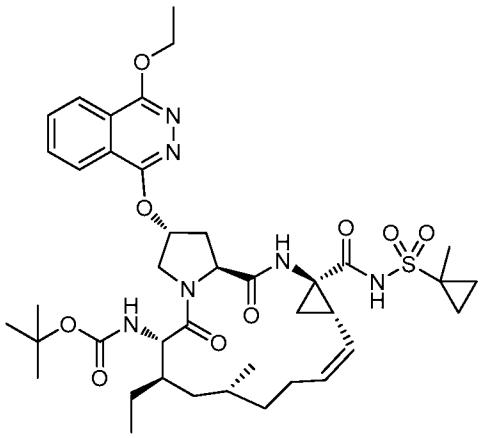
Compound 5044: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-ethoxyphthalazin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 837.3 (M^++1).

Compound 5045: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-ethoxyphthalazin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.20 (s, 1H), 9.04 (br. s., 1H), 8.13 (d, *J*=7.6 Hz, 1H), 8.04 - 7.93 (m, 3H), 7.86 (d, *J*=7.9 Hz, 1H), 5.85 (br. s., 1H), 5.54 (d, *J*=6.1 Hz, 1H), 5.06 (t, *J*=9.8 Hz, 1H), 4.66 - 4.46 (m, 4H), 3.99 - 3.81 (m, 2H), 2.99 - 2.87 (m, 1H), 2.72 - 2.63 (m, 2H), 2.40 - 2.22 (m, 2H), 2.01 - 1.87 (m, 2H), 1.62 - 1.31 (m, 13H), 1.18 - 1.12 (m, 3H), 1.05 - 0.91 (m, 9H), 0.73 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 837.3 (M^++1).

Preparation of Compound 5046 and Compound 5047



Compound 5046



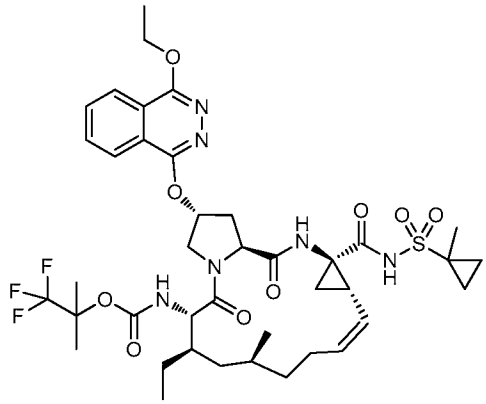
Compound 5047

Compound 5046 and Compound 5047 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

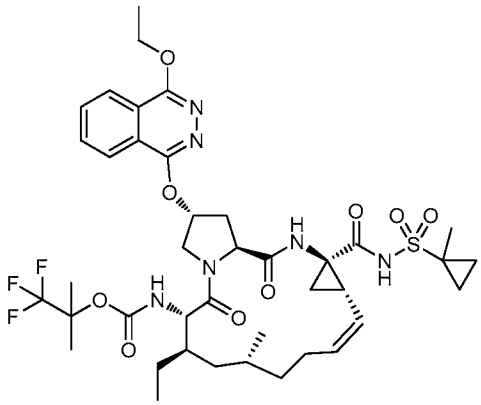
Compound 5046: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-ethoxyphthalazin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 797.4 (M^++1).

Compound 5047: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-ethoxyphthalazin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.06 (br. s., 1H), 9.13 (br. s., 1H), 8.11 (d, *J*=7.9 Hz, 1H), 8.07 - 7.88 (m, 3H), 7.18 (d, *J*=7.9 Hz, 1H), 5.85 (br. s., 1H), 5.52 (br. s., 1H), 4.99 (br. s., 1H), 4.70 (d, *J*=11.9 Hz, 1H), 4.62 - 4.48 (m, 3H), 3.99 - 3.83 (m, 2H), 2.68 (br. s., 2H), 2.38 - 2.27 (m, 2H), 1.97 - 1.86 (m, 2H), 1.61 (br. s., 1H), 1.56 - 1.39 (m, 10H), 1.39 - 1.30 (m, 2H), 1.26 (d, *J*=6.7 Hz, 2H), 1.16 (d, *J*=6.7 Hz, 1H), 1.07 - 0.96 (m, 10H), 0.95 - 0.85 (m, 5H), 0.73 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 797.4 (M^++1).

Preparation of Compound 5048 and Compound 5049



Compound 5048



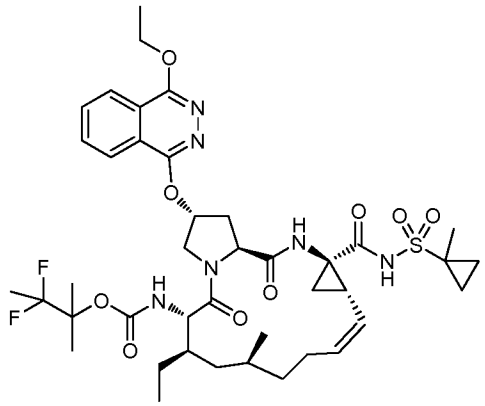
Compound 5049

Compound 5048 and Compound 5049 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

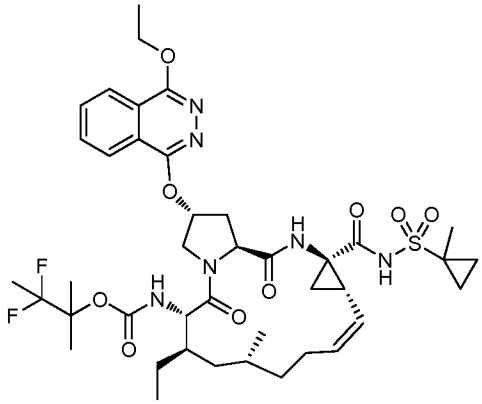
Compound 5048: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-ethoxyphthalazin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 851.4 (M^++1).

Compound 5049: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-ethoxyphthalazin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.17 (br. s., 1H), 8.13 (d, *J*=7.3 Hz, 1H), 8.04 - 7.93 (m, 3H), 7.86 (d, *J*=8.2 Hz, 1H), 5.86 (br. s., 1H), 5.53 (br. s., 1H), 4.98 (br. s., 1H), 4.68 - 4.50 (m, 4H), 4.01 - 3.79 (m, 2H), 2.69 (br. s., 2H), 2.41 - 2.24 (m, 2H), 1.99 - 1.85 (m, 2H), 1.63 (br. s., 1H), 1.57 - 1.40 (m, 11H), 1.36 (d, *J*=15.6 Hz, 2H), 1.30 (s, 4H), 1.17 (br. s., 1H), 1.02 (t, *J*=13.1 Hz, 1H), 0.96 - 0.84 (m, 8H), 0.73 (t, *J*=7.3 Hz, 3H); MS: MS *m/z* 851.4 (M^++1).

Preparation of Compound 5050 and Compound 5051



Compound 5050



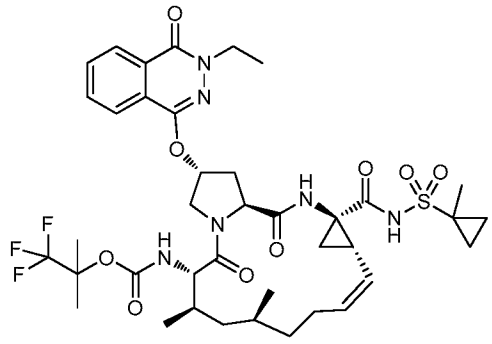
Compound 5051

Compound 5050 and Compound 5051 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

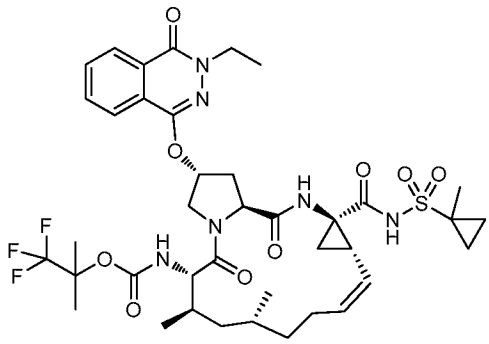
Compound 5050: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-ethoxyphthalazin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 847.4 (M^++1).

Compound 5051: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-ethoxyphthalazin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.06 (br. s., 1H), 9.14 (br. s., 1H), 8.13 (d, *J*=7.9 Hz, 1H), 8.06 - 7.92 (m, 3H), 7.64 (d, *J*=8.2 Hz, 1H), 5.86 (br. s., 1H), 5.60 - 5.48 (m, 1H), 4.98 (t, *J*=9.9 Hz, 1H), 4.68 - 4.49 (m, 4H), 3.99 - 3.81 (m, 2H), 2.77 - 2.64 (m, 2H), 2.41 - 2.26 (m, 2H), 1.92 (s, 2H), 1.62 (d, *J*=7.0 Hz, 1H), 1.60 - 1.39 (m, 15H), 1.39 - 1.28 (m, 2H), 1.20 (s, 4H), 1.03 (t, *J*=12.1 Hz, 1H), 0.96 - 0.87 (m, 5H), 0.84 (s, 3H), 0.74 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 847.4 (M^++1).

Preparation of Compound 5052 and Compound 5053



Compound 5052



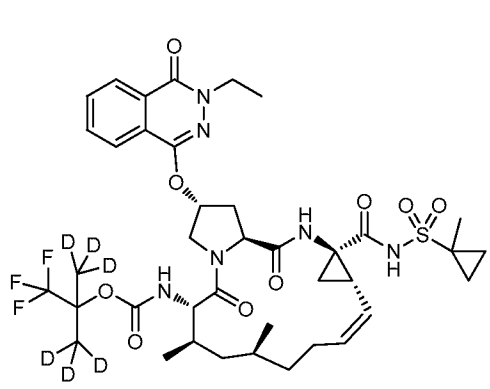
Compound 5053

Compound 5052 and Compound 5053 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

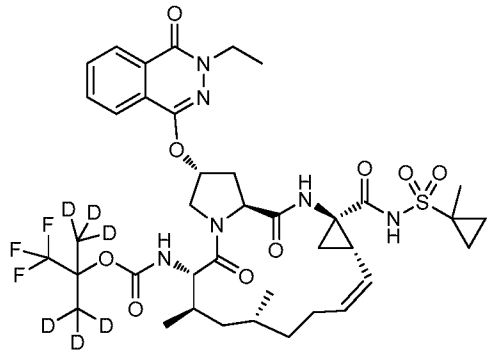
Compound 5052: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 837.3 (M^++1).

Compound 5053: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.06 (br. s., 1H), 9.02 (br. s., 1H), 8.29 - 8.23 (m, 1H), 7.96 - 7.87 (m, 3H), 7.79 (d, *J*=7.9 Hz, 1H), 5.53 (br. s., 1H), 5.49 (br. s., 1H), 5.06 (br. s., 1H), 4.67 (d, *J*=12.5 Hz, 1H), 4.56 - 4.43 (m, 1H), 4.22 - 4.10 (m, 1H), 4.01 (dq, *J*=13.3, 6.9 Hz, 1H), 3.93 - 3.83 (m, 1H), 3.68 (dd, *J*=10.7, 8.2 Hz, 1H), 2.62 (dd, *J*=13.6, 6.3 Hz, 2H), 2.35 - 2.23 (m, 2H), 1.94 - 1.77 (m, 2H), 1.72 - 1.64 (m, 1H), 1.59 (br. s., 1H), 1.47 (br. s., 1H), 1.39 (s, 5H), 1.36 - 1.29 (m, 7H), 1.27 - 1.17 (m, 1H), 1.15 (br. s., 1H), 0.95 - 0.82 (m, 11H), 0.73 (t, *J*=11.9 Hz, 1H); MS: MS *m/z* 837.3 (M^++1).

Preparation of Compound 5054 and Compound 5055



Compound 5054



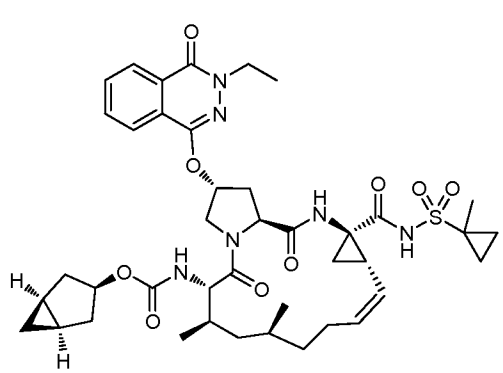
Compound 5055

Compound 5054 and Compound 5055 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

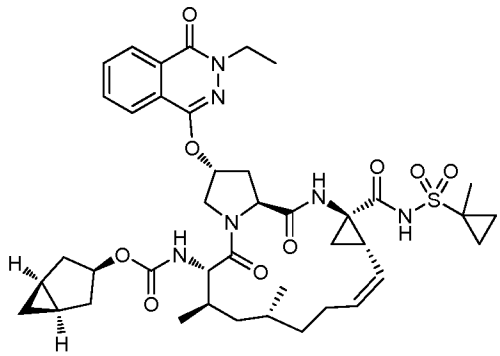
Compound 5054: MS: MS *m/z* 843.5 (M^++1).

Compound 5055: ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.04 (br. s., 1H), 9.17 (br. s., 1H), 8.31 - 8.24 (m, 1H), 7.95 - 7.86 (m, 3H), 7.83 (d, *J*=6.7 Hz, 1H), 5.54 (br. s., 2H), 4.99 (br. s., 1H), 4.67 (br. s., 1H), 4.51 (br. s., 1H), 4.16 (dd, *J*=13.4, 6.7 Hz, 1H), 4.03 (dd, *J*=13.0, 6.9 Hz, 1H), 3.95 - 3.82 (m, 1H), 3.70 (dd, *J*=10.7, 8.2 Hz, 1H), 2.65 (br. s., 2H), 2.36 - 2.23 (m, 2H), 1.92 -1.84 (d, *J*=7.0 Hz, 2H), 1.70 (br. s., 1H), 1.61 - 1.53 (m, 1H), 1.40 - 1.17 (m, 13H), 1.00 - 0.83 (m, 7H), 0.75 (br. s., 1H); MS: MS *m/z* 843.5 (M^++1).

Preparation of Compound 5056 and Compound 5057



Compound 5056



Compound 5057

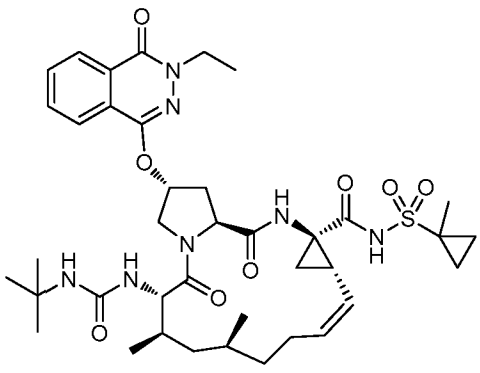
Compound 5056 and Compound 5057 were prepared using the intermediates

described herein and by following the general procedure described for the synthesis of Compound 3117:

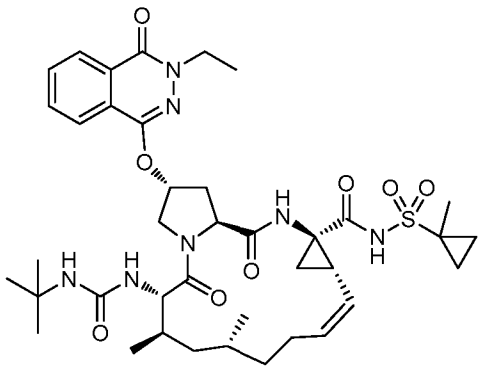
Compound 5056: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 807.4 (M^++1).

Compound 5057: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.04 (br. s., 1H), 8.84 (br. s., 1H), 8.33 - 8.21 (m, 1H), 7.97 - 7.85 (m, 3H), 7.34 (d, *J*=8.9 Hz, 1H), 5.53 (br. s., 1H), 5.47 (br. s., 1H), 5.12 (br. s., 1H), 4.60 (d, *J*=11.9 Hz, 1H), 4.51 - 4.38 (m, 2H), 4.13 - 3.99 (m, 2H), 3.92 - 3.84 (m, 1H), 3.79 - 3.66 (m, 1H), 2.65 - 2.54 (m, 2H), 2.32 - 2.19 (m, 2H), 1.97 - 1.86 (m, 3H), 1.80 (d, *J*=4.9 Hz, 1H), 1.64 (dd, *J*=8.5, 5.8 Hz, 2H), 1.53 (d, *J*=14.6 Hz, 2H), 1.38 (s, 6H), 1.35 - 1.28 (m, 5H), 1.23 (br. s., 1H), 1.21 - 1.10 (m, 3H), 1.05 - 0.98 (m, 1H), 0.91 (d, *J*=6.7 Hz, 3H), 0.85 (d, *J*=6.4 Hz, 3H), 0.77 - 0.66 (m, 2H), 0.32 - 0.21 (m, 2H); MS: MS *m/z* 807.4 (M^++1).

Preparation of Compound 5058 and Compound 5059



Compound 5058



Compound 5059

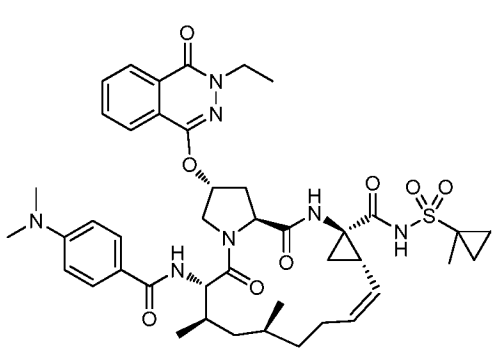
Compound 5058 and Compound 5059 were prepared using the intermediates

described herein and by following the general procedure described for the synthesis of Compound 3117:

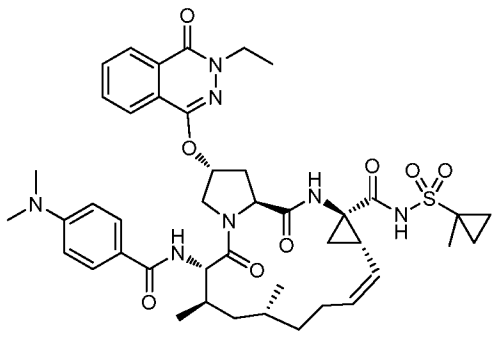
Compound 5058: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 782.4 (M^++1).

Compound 5059: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.04 (br. s., 1H), 8.84 (br. s., 1H), 8.23 (d, *J*=7.9 Hz, 1H), 7.95 - 7.81 (m, 3H), 5.88 (d, *J*=8.9 Hz, 1H), 5.52 (s, 2H), 5.46 (br. s., 1H), 4.70 (d, *J*=11.6 Hz, 1H), 4.42 (br. s., 1H), 4.18 - 4.00 (m, 2H), 3.95 - 3.77 (m, 2H), 2.60 - 2.54 (m, 1H), 2.32 - 2.23 (m, 2H), 1.95 - 1.83 (m, 1H), 1.65 (d, *J*=14.0 Hz, 2H), 1.55 (br. s., 1H), 1.45 - 1.15 (m, 13H), 0.97 - 0.71 (m, 19H); MS: MS *m/z* 782.4 (M^++1).

Preparation of Compound 5060 and Compound 5061



Compound 5060



Compound 5061

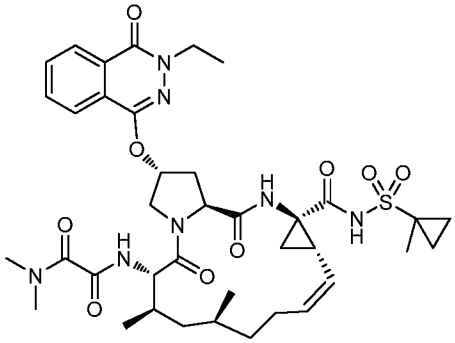
Compound 5060 and Compound 5061 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5060: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(4-(dimethylamino)benzamido)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-

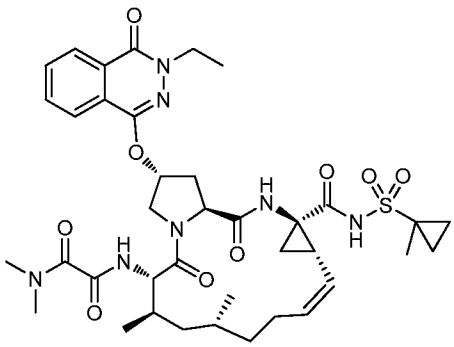
1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 830.4 (M^++1).

Compound 5061: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(4-(dimethylamino)benzamido)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.07 (br. s., 1H), 9.06 (br. s., 1H), 8.27 (d, *J*=7.6 Hz, 2H), 7.95 - 7.86 (m, 2H), 7.83 - 7.76 (m, 1H), 7.51 (d, *J*=8.9 Hz, 2H), 6.58 (d, *J*=9.2 Hz, 2H), 5.58 (br. s., 2H), 5.00 (br. s., 1H), 4.91 (d, *J*=9.5 Hz, 1H), 4.45 (br. s., 1H), 4.24 - 4.02 (m, 3H), 3.98 - 3.88 (m, 1H), 2.96 (s, 6H), 2.75 (br. s., 1H), 2.65 (br. s., 1H), 2.39 - 2.28 (m, 2H), 2.12 (d, *J*=5.8 Hz, 1H), 2.00 (br. s., 1H), 1.73 (br. s., 1H), 1.61 (br. s., 1H), 1.48 (br. s., 3H), 1.42 (br. s., 4H), 1.34 (t, *J*=7.2 Hz, 3H), 1.28 (br. s., 1H), 1.19 (br. s., 1H), 1.00 - 0.86 (m, 8H), 0.83 (d, *J*=11.0 Hz, 1H); MS: MS *m/z* 830.4 (M^++1).

Preparation of Compound 5062 and Compound 5063



Compound 5062



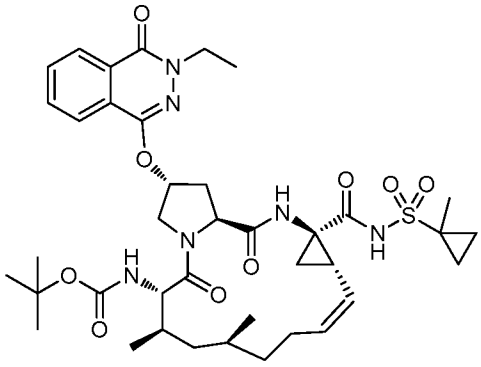
Compound 5063

Compound 5062 and Compound 5063 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

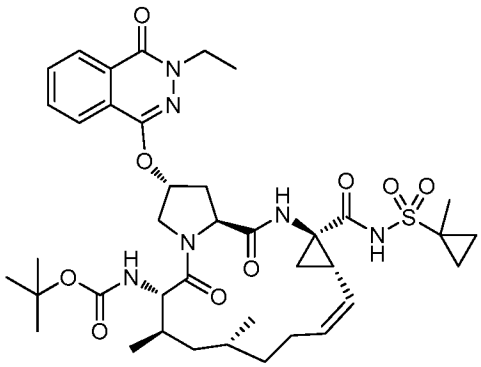
Compound 5062: N1-((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-N2,N2-dimethyloxalamide. MS: MS *m/z* 782.3 (M^++1).

Compound 5063: N1-((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-N2,N2-dimethyloxalamide. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.07 (br. s., 1H), 8.95 (d, *J*=7.9 Hz, 1H), 8.82 (s, 1H), 8.26 (dd, *J*=6.1, 3.1 Hz, 1H), 7.97 - 7.83 (m, 3H), 5.57 (br. s., 1H), 5.46 (br. s., 1H), 5.17 (br. s., 1H), 4.57 - 4.49 (m, 1H), 4.42 (t, *J*=8.5 Hz, 1H), 4.15 - 4.03 (m, 4H), 4.00 (d, *J*=8.5 Hz, 2H), 2.78 - 2.71 (m, 3H), 2.66 - 2.58 (m, 4H), 2.35 - 2.21 (m, 2H), 1.91 (s, 2H), 1.79 - 1.67 (m, 1H), 1.54 (br. s., 1H), 1.42 - 1.31 (m, 9H), 1.23 (br. s., 2H), 0.91 (d, *J*=7.6 Hz, 3H), 0.98 - 0.86 (m, 3H), 0.75 (d, *J*=10.7 Hz, 3H); MS: MS *m/z* 782.3 (M^++1).

Preparation of Compound 5064 and Compound 5065



Compound 5064



Compound 5065

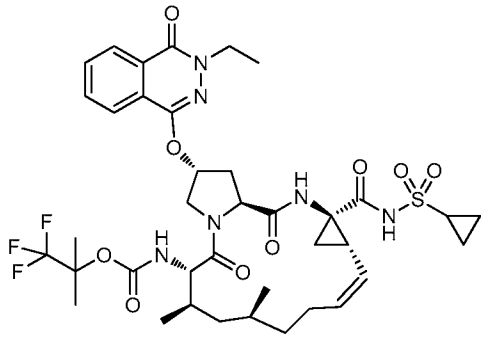
Compound 5064 and Compound 5065 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5064: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 783.4 (M^++1).

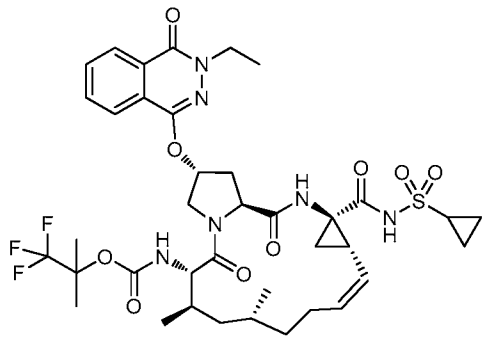
Compound 5065: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-

methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.06 (br. s., 1H), 9.14 (br. s., 1H), 8.31 - 8.23 (m, 1H), 7.94 - 7.82 (m, 3H), 7.19 (d, *J*=7.9 Hz, 1H), 5.60 - 5.48 (m, 2H), 4.97 (t, *J*=9.5 Hz, 1H), 4.76 (d, *J*=11.6 Hz, 1H), 4.51 (dd, *J*=10.4, 6.7 Hz, 1H), 4.22 - 4.10 (m, 1H), 4.09 - 3.96 (m, 1H), 3.94 - 3.86 (m, 1H), 3.70 (dd, *J*=10.7, 8.5 Hz, 1H), 2.75 - 2.59 (m, 2H), 2.40 - 2.21 (m, 2H), 1.97 - 1.77 (m, 2H), 1.72 - 1.58 (m, 2H), 1.55 - 1.38 (m, 6H), 1.38 - 1.24 (m, 5H), 1.18 - 1.06 (m, 2H), 1.04 (s, 8H), 0.96 - 0.85 (m, 8H), 0.74 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 783.4 (M^++1).

Preparation of Compound 5066 and Compound 5067



Compound 5066



Compound 5067

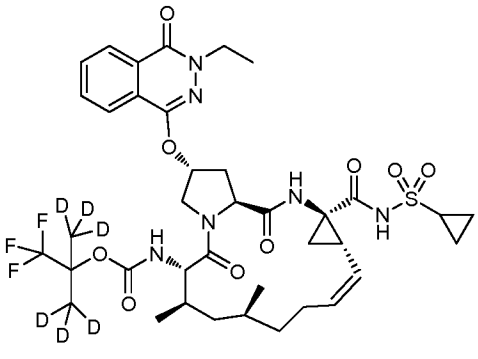
Compound 5066 and Compound 5067 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5066: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 823.3 (M^++1).

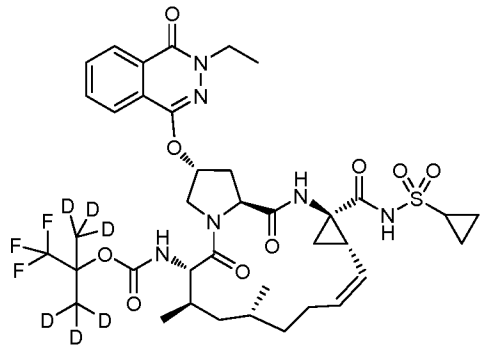
Compound 5067: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm

11.19 (br. s., 1H), 9.04 (br. s., 1H), 8.31 - 8.24 (m, 1H), 7.94 - 7.78 (m, 4H), 5.54 (br. s., 2H), 5.05 (br. s., 1H), 4.68 (d, *J*=11.6 Hz, 1H), 4.50 (dd, *J*=9.9, 7.2 Hz, 1H), 4.23 - 4.11 (m, 1H), 4.08 - 3.97 (m, 1H), 3.87 (dd, *J*=11.4, 2.9 Hz, 1H), 3.69 (dd, *J*=10.7, 7.9 Hz, 1H), 2.91 (d, *J*=7.6 Hz, 1H), 2.65 (dd, *J*=13.0, 6.6 Hz, 2H), 2.38 - 2.17 (m, 2H), 1.96 - 1.77 (m, 2H), 1.69 (dd, *J*=12.5, 6.7 Hz, 1H), 1.65 - 1.60 (m, 1H), 1.56 (br. s., 1H), 1.48 - 1.28 (m, 8H), 1.21 -1.13 (m, 3H), 1.04 - 0.85 (m, 11H), 0.75 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 823.3 (M^++1).

Preparation of Compound 5068 and Compound 5069



Compound 5068



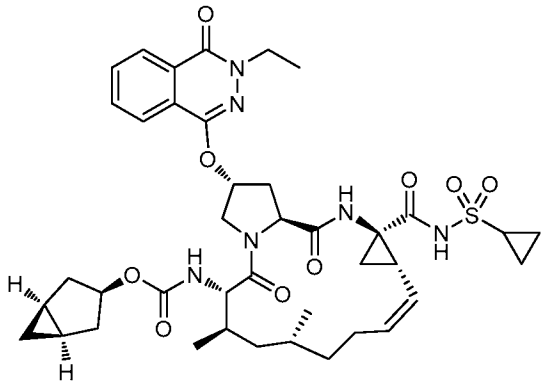
Compound 5069

Compound 5068 and Compound 5069 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5068: MS: MS *m/z* 829.5 (M^++1).

Compound 5069: ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.19 (br. s., 1H), 9.04 (br. s., 1H), 8.31 - 8.23 (m, 1H), 7.94 - 7.87 (m, 3H), 7.84 (d, *J*=7.6 Hz, 1H), 5.54 (br. s., 2H), 5.06 (br. s., 1H), 4.68 (d, *J*=11.6 Hz, 1H), 4.50 (dd, *J*=9.9, 7.2 Hz, 1H), 4.22 - 4.09 (m, 1H), 4.09 - 3.98 (m, 1H), 3.87 (dd, *J*=11.4, 2.9 Hz, 1H), 3.69 (dd, *J*=10.7, 7.9 Hz, 1H), 2.91 (d, *J*=4.9 Hz, 1H), 2.64 (dd, *J*=13.0, 6.3 Hz, 2H), 2.38 - 2.23 (m, 2H), 1.96 - 1.78 (m, 2H), 1.74 - 1.66 (m, 1H), 1.62 (br. s., 1H), 1.55 (br. s., 1H), 1.47 - 1.29 (m, 5H), 1.13 (br. s., 3H), 1.04 - 0.86 (m, 8H), 0.75 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 829.5 (M^++1).

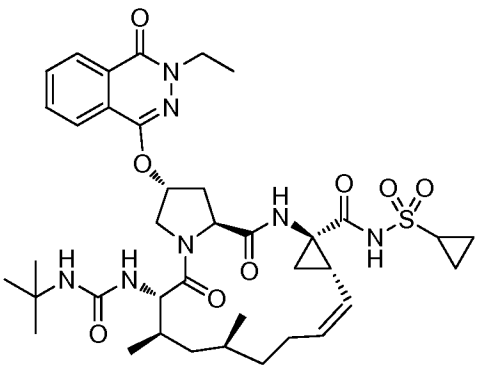
Preparation of Compound 5070



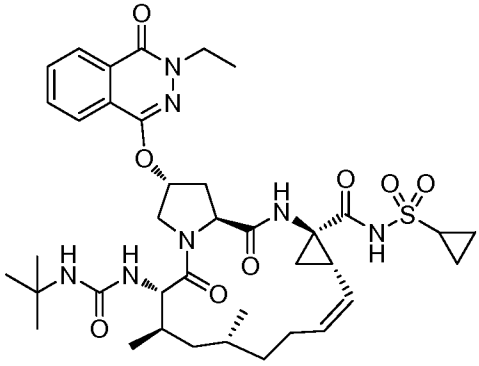
Compound 5070

Compound 5070 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117: Compound 5070: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 8.34 - 8.21 (m, 1H), 7.99 - 7.81 (m, 3H), 7.35 (d, *J*=8.5 Hz, 1H), 5.53 (br. s., 1H), 5.43 (br. s., 1H), 4.58 (d, *J*=11.6 Hz, 1H), 4.51 - 4.39 (m, 2H), 4.15 - 4.04 (m, 2H), 3.87 (dd, *J*=11.4, 3.2 Hz, 1H), 3.78 - 3.67 (m, 1H), 2.79 (br. s., 1H), 2.57 (d, *J*=9.5 Hz, 1H), 2.35 - 2.14 (m, 2H), 1.98 - 1.87 (m, 3H), 1.86 - 1.76 (m, 1H), 1.67 (dt, *J*=14.1, 5.8 Hz, 2H), 1.54 - 1.41 (m, 4H), 1.33 (t, *J*=7.2 Hz, 5H), 1.24 - 1.13 (m, 3H), 1.07 - 0.68 (m, 12H), 0.33 - 0.22 (m, 2H); MS: MS *m/z* 793.4 (M^++1).

Preparation of Compound 5071 and Compound 5072



Compound 5071



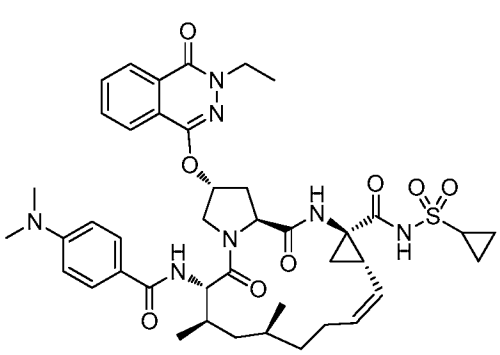
Compound 5072

Compound 5071 and Compound 5072 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

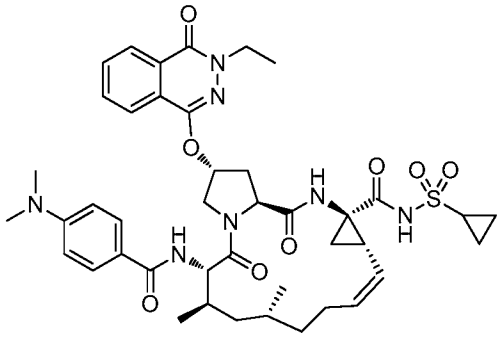
Compound 5071: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-N-(cyclopropylsulfonyl)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 768.4 (M^++1).

Compound 5072: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-N-(cyclopropylsulfonyl)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 8.70 (br. s., 1H), 8.24 (d, *J*=7.3 Hz, 1H), 7.98 - 7.75 (m, 3H), 5.90 (d, *J*=9.2 Hz, 1H), 5.57 - 5.51 (m, 2H), 5.48 - 5.37 (m, 1H), 5.26 (br. s., 1H), 4.69 (d, *J*=11.6 Hz, 1H), 4.40 (dd, *J*=9.8, 7.0 Hz, 1H), 4.18 - 3.99 (m, 2H), 3.93 - 3.77 (m, 2H), 2.82 (br. s., 1H), 2.64 - 2.54 (m, 1H), 2.34 - 2.15 (m, 2H), 1.96 - 1.85 (m, 2H), 1.76 - 1.60 (m, 2H), 1.54 (dd, *J*=8.1, 4.4 Hz, 1H), 1.48 - 1.37 (m, 2H), 1.37 - 1.26 (m, 4H), 1.25 - 1.13 (m, 1H), 1.01 - 0.85 (m, 18H), 0.70 (t, *J*=11.3 Hz, 1H); MS: MS *m/z* 768.4 (M^++1).

Preparation of Compound 5073 and Compound 5074



Compound 5073



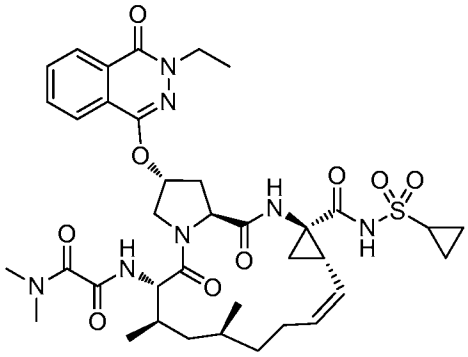
Compound 5074

Compound 5073 and Compound 5074 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

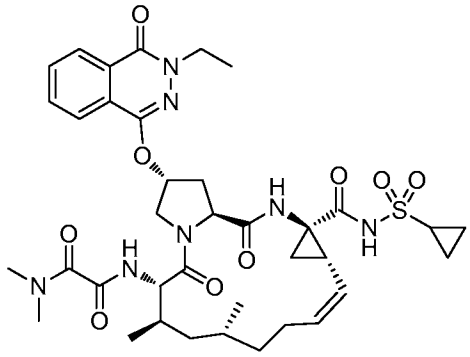
Compound 5073: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(4-(dimethylamino)benzamido)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 816.4 (M^++1).

Compound 5074: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(4-(dimethylamino)benzamido)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.21 (br. s., 1H), 8.92 (br. s., 1H), 8.34 - 8.19 (m, 2H), 7.96 - 7.87 (m, 2H), 7.84 - 7.78 (m, 1H), 7.52 (d, *J*=8.9 Hz, 2H), 6.58 (d, *J*=9.2 Hz, 2H), 5.65 - 5.46 (m, 2H), 5.08 (br. s., 1H), 4.88 (d, *J*=10.7 Hz, 1H), 4.42 (t, *J*=8.2 Hz, 1H), 4.24 - 4.02 (m, 3H), 3.96 - 3.86 (m, 1H), 2.96 (s, 6H), 2.90 (s, 1H), 2.65 (br. s., 2H), 2.37 - 2.25 (m, 2H), 2.11 (d, *J*=6.4 Hz, 1H), 2.01 (br. s., 1H), 1.76 (d, *J*=9.8 Hz, 1H), 1.59 (br. s., 1H), 1.51 (br. s., 2H), 1.41 (br. s., 1H), 1.34 (t, *J*=7.2 Hz, 3H), 1.20 (br. s., 1H), 1.08 (d, *J*=7.3 Hz, 2H), 0.95 (t, *J*=7.3 Hz, 8H), 0.80 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 816.4 (M^++1).

Preparation of Compound 5075 and Compound 5076



Compound 5075



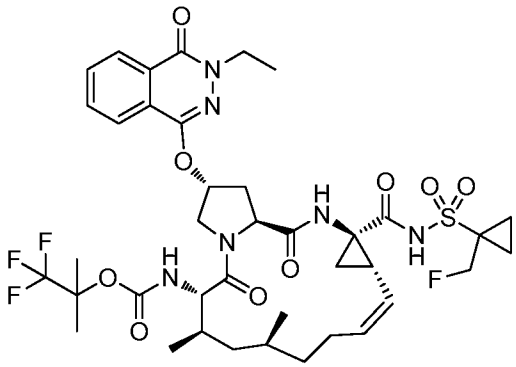
Compound 5076

Compound 5075 and Compound 5076 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5075: N1-((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-N2,N2-dimethyloxalamide. MS: MS *m/z* 768.3 (M^++1).

Compound 5076: N1-((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-N2,N2-dimethyloxalamide. MS: MS *m/z* 768.3 (M^++1).

Preparation of Compound 5077

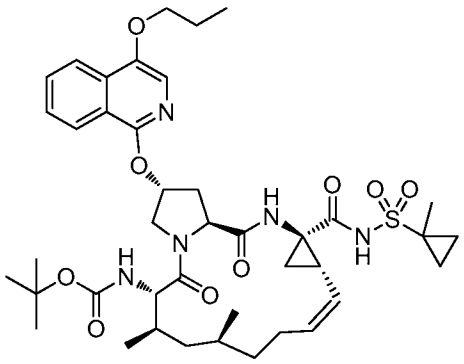


Compound 5077

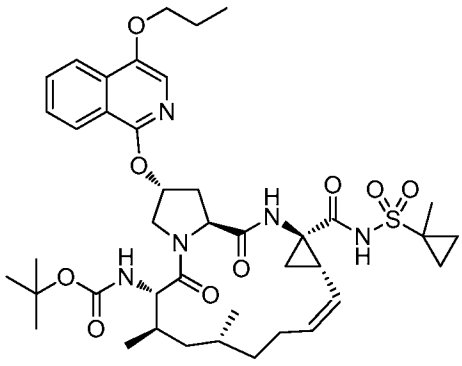
Compound 5077 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5077: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.28 (s, 1H), 9.09 (br. s., 1H), 8.27 (dd, *J*=6.1, 2.7 Hz, 1H), 7.94 - 7.87 (m, 3H), 7.84 (d, *J*=7.9 Hz, 1H), 5.64 - 5.46 (m, 2H), 4.99 (t, *J*=9.8 Hz, 1H), 4.69 (d, *J*=11.9 Hz, 1H), 4.61 (d, *J*=11.6 Hz, 1H), 4.51 (d, *J*=11.0 Hz, 1H), 4.23 - 4.13 (m, 1H), 4.08 - 3.96 (m, 1H), 3.93 - 3.83 (m, 1H), 3.70 (dd, *J*=10.7, 7.9 Hz, 1H), 2.72 - 2.57 (m, 2H), 2.37 - 2.23 (m, 2H), 1.96 - 1.79 (m, 2H), 1.66 (d, *J*=14.0 Hz, 1H), 1.55 (d, *J*=11.0 Hz, 4H), 1.42 (br. s., 1H), 1.39 - 1.30 (m, 7H), 1.30 - 1.14 (m, 4H), 0.99 - 0.85 (m, 9H), 0.82 - 0.71 (m, 1H); MS: MS *m/z* 855.33 (M^++1).

Preparation of Compound 5078 and Compound 5079



Compound 5078



Compound 5079

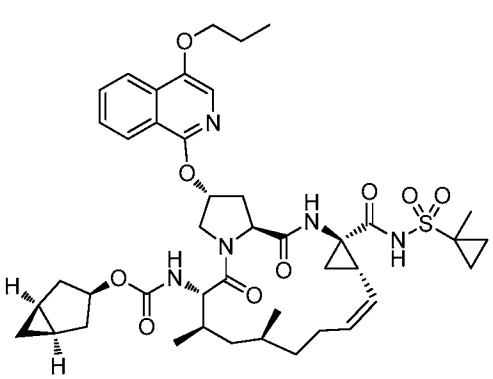
Compound 5078 and Compound 5079 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5078: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

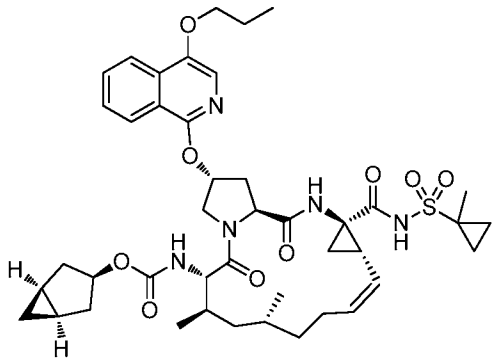
hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 796.4 (M^++1).

Compound 5079: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.06 (s, 1H), 9.11 (s, 1H), 8.08 (d, *J*=8.2 Hz, 1H), 8.11 (d, *J*=8.2 Hz, 1H), 7.79 (t, *J*=7.6 Hz, 1H), 7.64 (s, 1H), 7.59 (t, *J*=7.8 Hz, 1H), 7.18 (d, *J*=8.2 Hz, 1H), 5.76 (br. s., 1H), 5.58 - 5.47 (m, 1H), 4.97 (t, *J*=9.9 Hz, 1H), 4.61 (d, *J*=11.3 Hz, 1H), 4.49 (dd, *J*=10.1, 7.0 Hz, 1H), 4.17 - 4.05 (m, 2H), 3.95 - 3.86 (m, 1H), 3.72 (dd, *J*=10.5, 8.4 Hz, 1H), 2.76 - 2.66 (m, 1H), 2.61 (dd, *J*=13.9, 6.3 Hz, 1H), 2.40 - 2.25 (m, 2H), 1.96 - 1.78 (m, 4H), 1.69 (dd, *J*=12.7, 6.9 Hz, 1H), 1.64 - 1.58 (m, 1H), 1.51 (dd, *J*=9.0, 5.0 Hz, 1H), 1.48 - 1.21 (m, 7H), 1.18 - 1.02 (m, 13H), 0.95 - 0.85 (m, 8H), 0.74 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 796.4 (M^++1).

Preparation of Compound 5080 and Compound 5081



Compound 5080



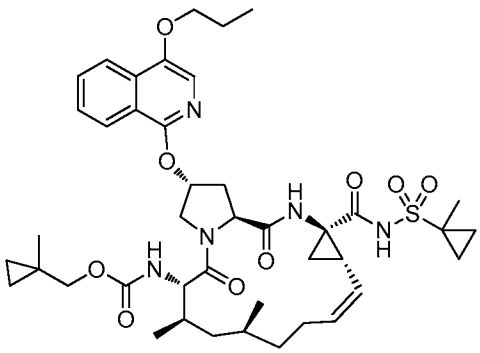
Compound 5081

Compound 5080 and Compound 5081 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

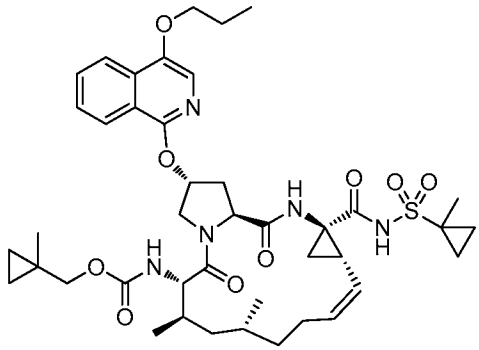
Compound 5080: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 820.4 (M^++1).

Compound 5081: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.07 (br. s., 1H), 8.09 (d, *J*=8.9 Hz, 2H), 7.85 - 7.75 (m, 1H), 7.68 - 7.61 (m, 2H), 7.40 (d, *J*=8.5 Hz, 1H), 5.78 (br. s., 1H), 5.52 (br. s., 1H), 4.98 (br. s., 1H), 4.59 (t, *J*=6.7 Hz, 1H), 4.48 (d, *J*=5.2 Hz, 2H), 4.12 (t, *J*=6.4 Hz, 2H), 3.94 (dd, *J*=12.1, 4.1 Hz, 1H), 3.81 - 3.61 (m, 1H), 2.77 - 2.68 (m, 1H), 2.61 (br. s., 1H), 2.35 - 2.19 (m, 2H), 1.98 - 1.80 (m, 5H), 1.79 - 1.71 (m, 1H), 1.69 - 1.54 (m, 3H), 1.51 (br. s., 2H), 1.41 (s, 5H), 1.37 - 1.16 (m, 3H), 1.15 - 1.06 (m, 5H), 0.96 - 0.85 (m, 8H), 0.74 (t, *J*=12.4 Hz, 1H), 0.37 - 0.29 (m, 2H); MS: MS *m/z* 820.4 (M^++1).

Preparation of Compound 5082 and Compound 5083



Compound 5082



Compound 5083

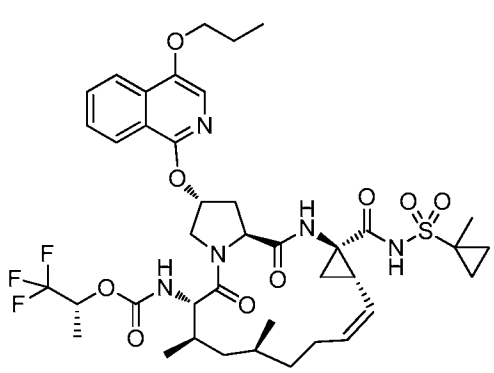
Compound 5082 and Compound 5083 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5082: (1-methylcyclopropyl)methyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 808.8 (M^++1).

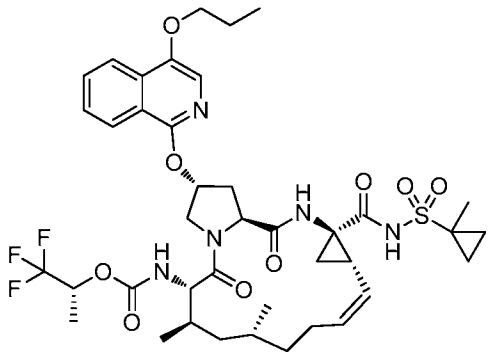
Compound 5083: (1-methylcyclopropyl)methyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-

propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (s, 1H), 9.09 (br. s., 1H), 8.09 (d, *J*=8.2 Hz, 2H), 7.80 (t, *J*=7.6 Hz, 1H), 7.66 - 7.58 (m, 2H), 7.50 (d, *J*=8.2 Hz, 1H), 5.79 (br. s., 1H), 5.61 - 5.44 (m, 1H), 4.98 (t, *J*=9.6 Hz, 1H), 4.60 - 4.41 (m, 2H), 4.12 (t, *J*=6.4 Hz, 2H), 3.97 - 3.90 (m, 1H), 3.76 (dd, *J*=10.5, 8.7 Hz, 1H), 2.76 - 2.68 (m, 1H), 2.61 (dd, *J*=13.1, 6.7 Hz, 1H), 2.40 - 2.22 (m, 2H), 1.97 - 1.81 (m, 4H), 1.68 (dd, *J*=13.0, 6.3 Hz, 1H), 1.61 (d, *J*=6.7 Hz, 1H), 1.51 (br. s., 1H), 1.48 - 1.39 (m, 6H), 1.39 - 1.32 (m, 1H), 1.32 - 1.24 (m, 1H), 1.18 - 1.05 (m, 4H), 0.97 - 0.86 (m, 12H), 0.80 - 0.70 (m, 1H), 0.29 - 0.12 (m, 4H); MS: MS *m/z* 808.7 (M^++1).

Preparation of Compound 5084 and Compound 5085



Compound 5084



Compound 5085

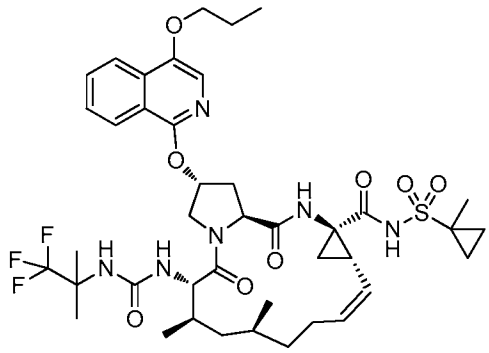
Compound 5084 and Compound 5085 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5084: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 836.7 (M^++1).

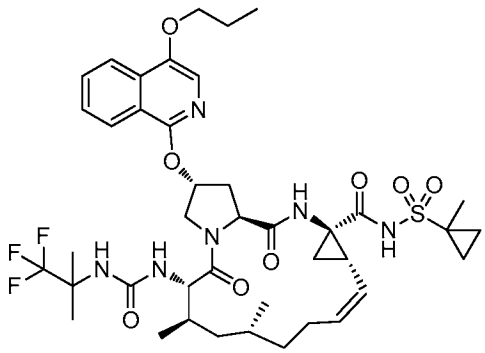
Compound 5085: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.03 (br. s., 1H), 9.10 (br. s., 1H), 8.06 (d,

J=8.5 Hz, 1H), 8.09 (d, *J*=8.2 Hz, 2H), 7.83 - 7.76 (m, 1H), 7.66 - 7.61 (m, 1H), 7.59 - 7.51 (m, 1H), 5.53 (br. s., 1H), 4.98 (br. s., 1H), 4.68 (dt, *J*=13.5, 6.8 Hz, 1H), 4.56 - 4.43 (m, 2H), 4.16 - 4.07 (m, 2H), 3.99 - 3.87 (m, 1H), 3.78 (dd, *J*=10.7, 8.2 Hz, 1H), 2.73 - 2.57 (m, 2H), 2.37 - 2.22 (m, 2H), 1.96 - 1.81 (m, 4H), 1.68 (d, *J*=6.7 Hz, 1H), 1.61 (br. s., 1H), 1.52 (br. s., 1H), 1.41 - 1.23 (m, 8H), 1.21 - 1.12 (m, 4H), 1.08 (t, *J*=7.3 Hz, 3H), 0.96 - 0.87 (m, 8H), 0.82 - 0.70 (m, 1H); MS: MS *m/z* 836.7 (M^++1).

Preparation of Compound 5086 and Compound 5087



Compound 5086



Compound 5087

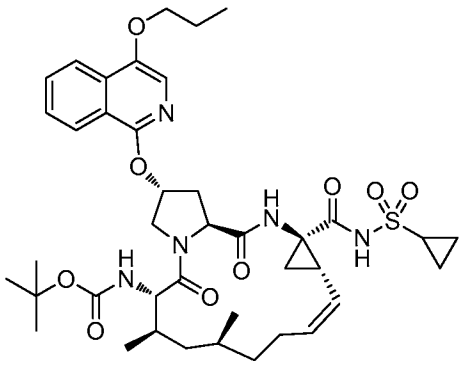
Compound 5086 and Compound 5087 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5086: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-6-(3-(1,1,1-trifluoro-2-methylpropan-2-yl)ureido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 849.7 (M^++1).

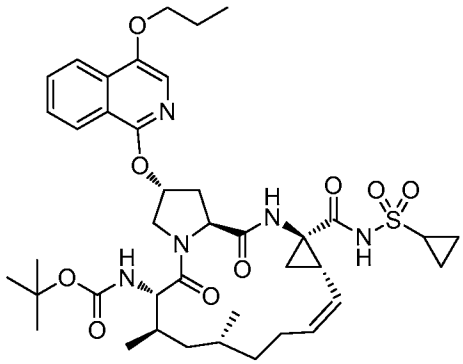
Compound 5087: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-6-(3-(1,1,1-trifluoro-2-methylpropan-2-yl)ureido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.04 (br. s., 1H), 9.09 (br. s., 1H), 8.09 (t, *J*=7.2 Hz, 2H), 7.80 (t, *J*=7.6 Hz, 1H), 7.64 (s, 1H), 7.59 (t, *J*=7.5 Hz, 1H), 6.24 (d, *J*=8.5 Hz, 1H), 6.07 (s, 1H), 5.77 (br. s., 1H), 5.53 (d, *J*=5.2 Hz, 1H), 4.98 (t, *J*=10.1 Hz, 1H), 4.56 - 4.40 (m, 2H), 4.18 - 4.05 (m, 2H), 3.97 - 3.89 (m, 1H), 3.85 (t, *J*=9.6 Hz, 1H), 2.75 - 2.66 (m, 1H), 2.66 -

2.56 (m, 1H), 2.42 - 2.18 (m, 2H), 1.96 - 1.82 (m, 3H), 1.75 - 1.64 (m, 2H), 1.61 (br. s., 1H), 1.51 (br. s., 1H), 1.47 - 1.39 (m, 5H), 1.39 - 1.33 (m, 1H), 1.33 - 1.23 (m, 1H), 1.18 (s, 4H), 1.21 (s, 3H), 1.10 - 1.04 (m, 3H), 0.92 (dd, *J*=15.0, 6.7 Hz, 8H), 0.76 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 849.7 (M^++1).

Preparation of Compound 5088 and Compound 5089



Compound 5088



Compound 5089

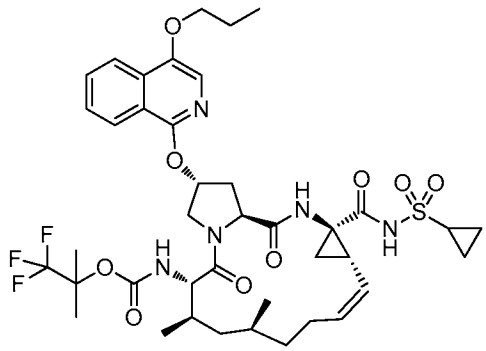
Compound 5088 and Compound 5089 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5088: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 782.7 (M^++1).

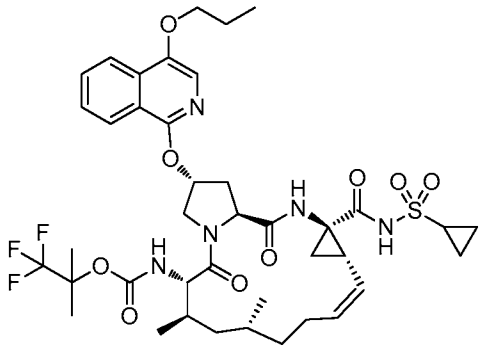
Compound 5089: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.20 (br. s., 1H), 8.98 (br. s., 1H), 8.08 (d, *J*=8.5 Hz, 1H), 8.11 (d, *J*=8.2 Hz, 1H), 7.79 (t, *J*=7.6 Hz, 1H), 7.64 (s, 1H), 7.59 (t, *J*=7.5 Hz, 1H), 7.16 (d, *J*=7.6 Hz, 1H), 5.75 (br. s., 1H), 5.52 (br. s., 1H), 5.04 (br. s., 1H), 4.60 (d, *J*=10.7 Hz, 1H), 4.45 (br. s., 1H), 4.17 - 4.06 (m, 2H), 3.93 - 3.85 (m, 1H), 3.77 - 3.66 (m, 1H), 2.91 (s, 1H), 2.75 - 2.58 (m, 2H), 2.35 - 2.24 (m, 2H), 1.96 - 1.77 (m, 4H), 1.70 (br. s., 1H), 1.60 (br. s., 1H), 1.54 (br. s., 1H), 1.48 - 1.31 (m, 2H),

1.18 - 1.04 (m, 15H), 1.00 (br. s., 1H), 0.94 (d, *J*=7.0 Hz, 4H), 0.88 (d, *J*=6.4 Hz, 3H), 0.77 - 0.68 (m, 1H); MS: MS *m/z* 782.7 (M^++1).

Preparation of Compound 5090 and Compound 5091



Compound 5090



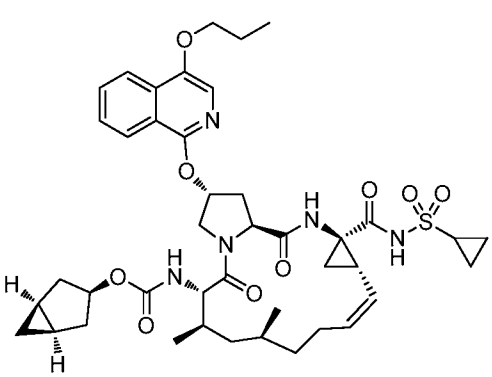
Compound 5091

Compound 5090 and Compound 5091 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

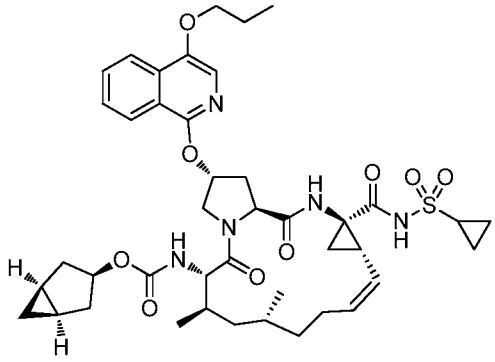
Compound 5090: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 836.7 (M^++1).

Compound 5091: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.20 (br. s., 1H), 9.01 (br. s., 1H), 8.09 (d, *J*=8.9 Hz, 2H), 7.84 - 7.77 (m, 2H), 7.67 - 7.60 (m, 2H), 5.75 (br. s., 1H), 5.52 (br. s., 1H), 5.06 (br. s., 1H), 4.62 - 4.45 (m, 2H), 4.18 - 4.07 (m, 2H), 3.93 - 3.85 (m, 1H), 3.70 (dd, *J*=10.7, 7.9 Hz, 1H), 2.91 (br. s., 1H), 2.62 (br. s., 2H), 2.31 (ddd, *J*=13.7, 10.2, 3.8 Hz, 2H), 1.86 (dq, *J*=13.8, 7.0 Hz, 4H), 1.72 (br. s., 1H), 1.60 (br. s., 1H), 1.55 (br. s., 1H), 1.47 - 1.29 (m, 5H), 1.28 - 1.03 (m, 10H), 0.94 (d, *J*=6.7 Hz, 4H), 0.89 (d, *J*=6.4 Hz, 3H), 0.73 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 836.8 (M^++1).

Preparation of Compound 5092 and Compound 5093



Compound 5092



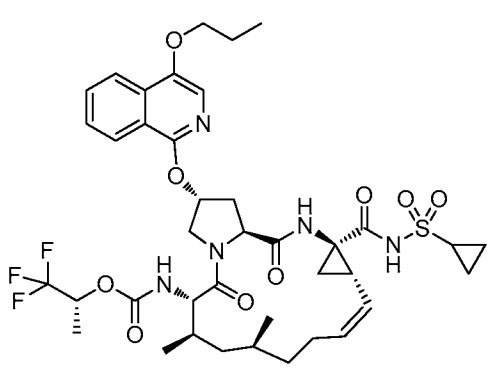
Compound 5093

Compound 5092 and Compound 5093 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

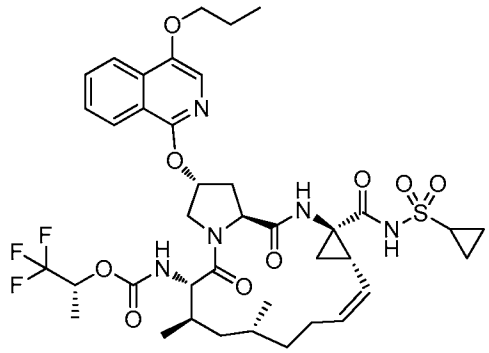
Compound 5092: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 806.7 (M^++1).

Compound 5093: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.19 (br. s., 1H), 8.95 (br. s., 1H), 8.10 (d, *J*=9.2 Hz, 2H), 7.81 (t, *J*=8.1 Hz, 1H), 7.68 - 7.60 (m, 2H), 7.38 (d, *J*=8.5 Hz, 1H), 5.77 (br. s., 1H), 5.52 (br. s., 1H), 5.06 (br. s., 1H), 4.61 (t, *J*=6.6 Hz, 1H), 4.52 - 4.39 (m, 2H), 4.12 (t, *J*=6.4 Hz, 2H), 3.96 - 3.86 (m, 1H), 3.81 - 3.68 (m, 1H), 2.91 (br. s., 1H), 2.73 (d, *J*=18.3 Hz, 1H), 2.61 (br. s., 1H), 2.35 - 2.24 (m, 2H), 1.98 - 1.74 (m, 6H), 1.66 (br. s., 1H), 1.57 (d, *J*=14.3 Hz, 3H), 1.44 (br. s., 1H), 1.41 - 1.30 (m, 2H), 1.26 - 1.06 (m, 8H), 0.93 (d, *J*=7.0 Hz, 5H), 0.87 (d, *J*=6.4 Hz, 3H), 0.72 (t, *J*=12.4 Hz, 1H), 0.38 - 0.30 (m, 2H); MS: MS *m/z* 806.7 (M^++1).

Preparation of Compound 5094 and Compound 5095



Compound 5094



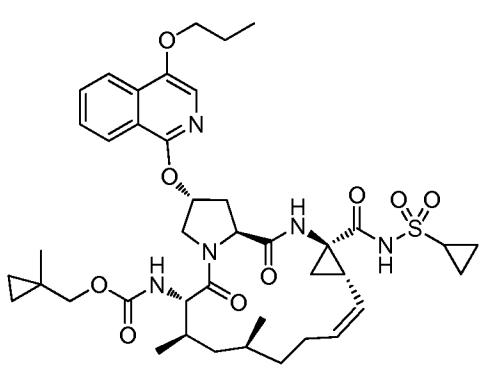
Compound 5095

Compound 5094 and Compound 5095 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

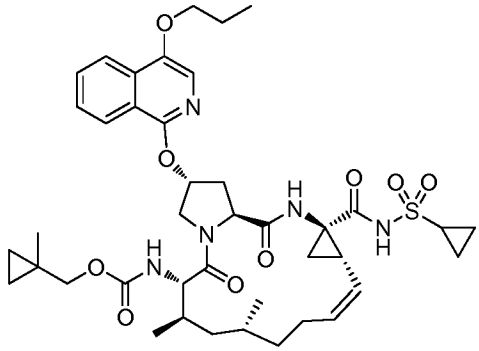
Compound 5094: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 822.7 (M^++1).

Compound 5095: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.18 (br. s., 1H), 8.97 (br. s., 1H), 8.12 - 8.03 (m, 3H), 7.80 (t, *J*=7.6 Hz, 1H), 7.64 (s, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 5.77 (br. s., 1H), 5.52 (br. s., 1H), 5.06 (br. s., 1H), 4.71 (dt, *J*=13.6, 6.9 Hz, 1H), 4.54 - 4.39 (m, 2H), 4.12 (t, *J*=6.4 Hz, 2H), 3.96 - 3.89 (m, 1H), 3.83 - 3.72 (m, 1H), 2.91 (br. s., 1H), 2.65 (br. s., 2H), 2.35 - 2.24 (m, 2H), 1.98 - 1.82 (m, 4H), 1.71 (br. s., 1H), 1.59 (br. s., 1H), 1.55 (br. s., 1H), 1.44 (br. s., 1H), 1.38 (d, *J*=14.3 Hz, 1H), 1.20 (d, *J*=6.7 Hz, 3H), 1.08 (t, *J*=7.3 Hz, 6H), 1.00 (d, *J*=6.4 Hz, 2H), 0.94 (d, *J*=6.7 Hz, 3H), 0.92 - 0.87 (m, 3H), 0.76 (t, *J*=11.9 Hz, 1H); MS: MS *m/z* 822.7 (M^++1).

Preparation of Compound 5096 and Compound 5097



Compound 5096



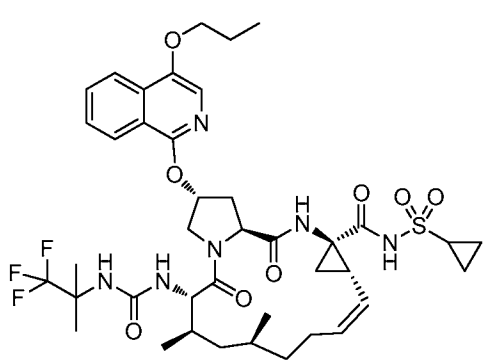
Compound 5097

Compound 5096 and Compound 5097 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

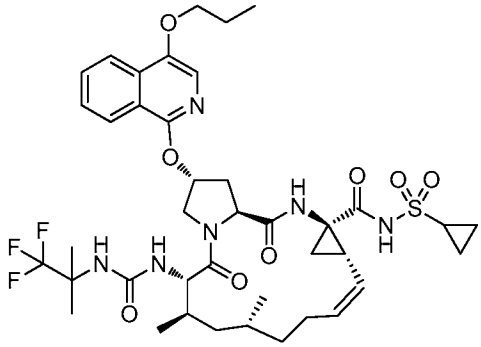
Compound 5096: (1-methylcyclopropyl)methyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 794.7 (M^++1).

Compound 5097: (1-methylcyclopropyl)methyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.19 (br. s., 1H), 8.96 (br. s., 1H), 8.09 (dd, *J*=8.2, 3.7 Hz, 2H), 7.80 (t, *J*=7.8 Hz, 1H), 7.67 - 7.58 (m, 2H), 7.49 (d, *J*=8.2 Hz, 1H), 5.77 (br. s., 1H), 5.52 (br. s., 1H), 5.06 (br. s., 1H), 4.57 - 4.41 (m, 2H), 4.12 (t, *J*=6.4 Hz, 2H), 3.96 - 3.88 (m, 1H), 3.83 - 3.73 (m, 1H), 2.91 (br. s., 1H), 2.69 (br. s., 1H), 2.60 (br. s., 1H), 2.30 (t, *J*=9.8 Hz, 2H), 1.99 - 1.80 (m, 5H), 1.70 (br. s., 1H), 1.60 (br. s., 1H), 1.54 (br. s., 1H), 1.48 - 1.28 (m, 2H), 1.08 (t, *J*=7.3 Hz, 7H), 1.01 - 0.87 (m, 11H), 0.80 - 0.70 (m, 1H), 0.31 - 0.14 (m, 4H); MS: MS *m/z* 794.7 (M^++1).

Preparation of Compound 5098 and Compound 5099



Compound 5098



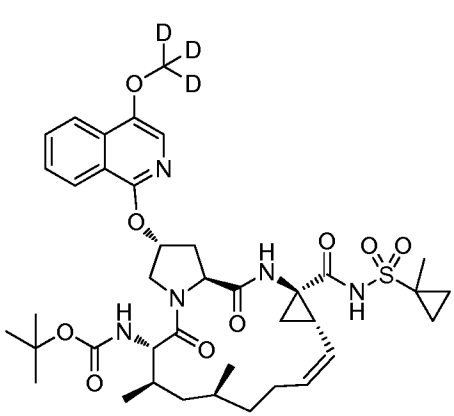
Compound 5099

Compound 5098 and Compound 5099 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

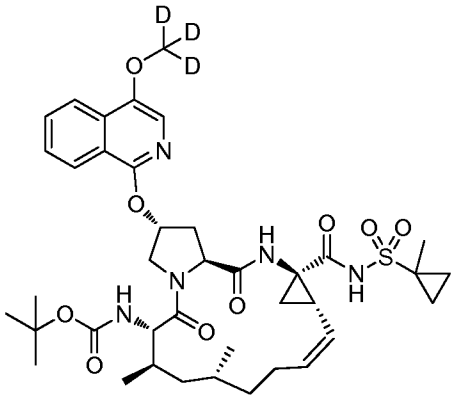
Compound 5098: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-7,9-dimethyl-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-6-(3-(1,1,1-trifluoro-2-methylpropan-2-yl)ureido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 835.7 (M^++1).

Compound 5099: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-7,9-dimethyl-5,16-dioxo-2-((4-propoxyisoquinolin-1-yl)oxy)-6-(3-(1,1,1-trifluoro-2-methylpropan-2-yl)ureido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.18 (br. s., 1H), 8.96 (br. s., 1H), 8.14 - 8.05 (m, 2H), 7.80 (t, *J*=7.6 Hz, 1H), 7.64 (s, 1H), 7.59 (t, *J*=7.8 Hz, 1H), 6.23 (d, *J*=8.2 Hz, 1H), 6.08 (s, 1H), 5.75 (br. s., 1H), 5.51 (br. s., 1H), 5.07 (br. s., 1H), 4.49 (br. s., 1H), 4.46 - 4.35 (m, 1H), 4.17 - 4.05 (m, 2H), 3.97 - 3.77 (m, 2H), 2.91 (s, 1H), 2.67 (d, *J*=16.2 Hz, 1H), 2.60 (br. s., 1H), 2.35 - 2.25 (m, 2H), 1.96 - 1.82 (m, 3H), 1.73 - 1.37 (m, 7H), 1.25 - 1.17 (m, 6H), 1.14 - 1.05 (m, 5H), 0.92 (dd, *J*=18.3, 6.7 Hz, 8H), 0.78 - 0.70 (m, 1H); MS: MS *m/z* 835.7 (M^++1).

Preparation of Compound 5100 and Compound 5101



Compound 5100



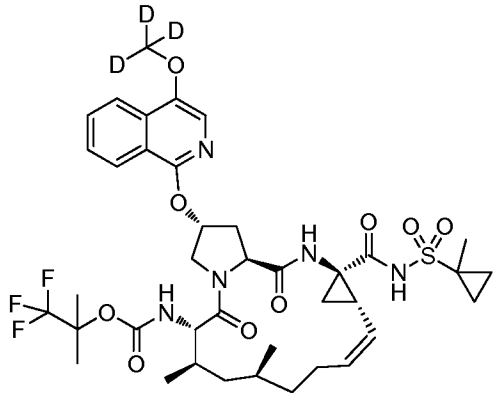
Compound 5101

Compound 5100 and Compound 5101 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

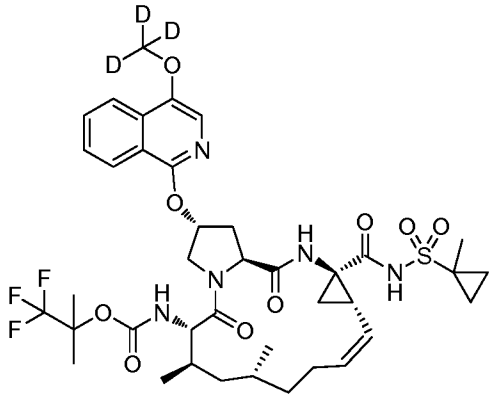
Compound 5100: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-(trideuteromethoxy)isoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 771.6 (M^++1).

Compound 5101: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-(trideuteromethoxy)isoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.06 (br. s., 1H), 9.10 (br. s., 1H), 8.12 (d, *J*=8.2 Hz, 1H), 8.06 (d, *J*=8.5 Hz, 1H), 7.79 (t, *J*=7.8 Hz, 1H), 7.65 (s, 1H), 7.60 (t, *J*=7.5 Hz, 1H), 7.17 (br. s., 1H), 5.77 (br. s., 1H), 5.52 (br. s., 1H), 4.96 (br. s., 1H), 4.59 (br. s., 1H), 4.48 (br. s., 1H), 3.96 - 3.87 (m, 1H), 3.77 - 3.66 (m, 1H), 2.76 - 2.66 (m, 1H), 2.60 (br. s., 1H), 2.41 - 2.24 (m, 2H), 1.91 (d, *J*=13.7 Hz, 1H), 1.83 (br. s., 1H), 1.70 (br. s., 1H), 1.60 (br. s., 1H), 1.50 (br. s., 1H), 1.40 (br. s., 5H), 1.28 (br. s., 2H), 1.12 (s, 10H), 0.98 - 0.84 (m, 8H), 0.74 (d, *J*=10.1 Hz, 1H); MS: MS *m/z* 771.6 (M^++1).

Preparation of Compound 5102 and Compound 5103



Compound 5102



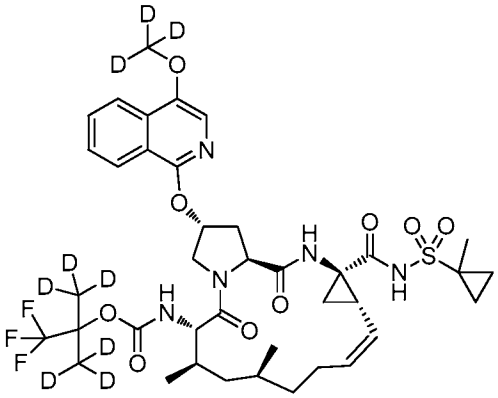
Compound 5103

Compound 5102 and Compound 5103 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

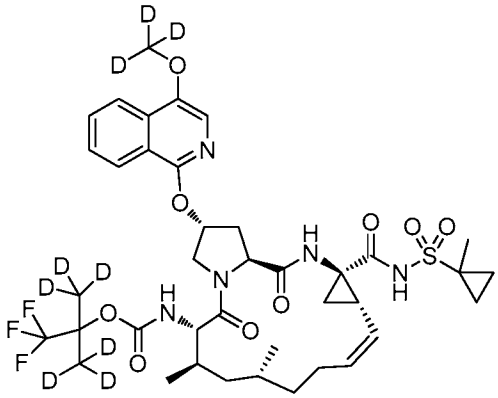
Compound 5102: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-(trideuteromethoxy)isoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 825.7 (M^++1).

Compound 5103: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-(trideuteromethoxy)isoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.14 (br. s., 1H), 8.07 (d, *J*=8.2 Hz, 1H), 8.10 (d, *J*=8.2 Hz, 1H), 7.87 - 7.75 (m, 2H), 7.67 - 7.57 (m, 2H), 5.78 (br. s., 1H), 5.53 (br. s., 1H), 4.97 (br. s., 1H), 4.62 - 4.43 (m, 2H), 3.97 - 3.86 (m, 1H), 3.70 (dd, *J*=10.7, 7.9 Hz, 1H), 2.74 - 2.57 (m, 2H), 2.36 - 2.25 (m, 2H), 1.96 - 1.79 (m, 2H), 1.70 (d, *J*=6.7 Hz, 1H), 1.62 (br. s., 1H), 1.51 (d, *J*=7.6 Hz, 1H), 1.41 (s, 5H), 1.39 - 1.25 (m, 5H), 1.16 (br. s., 1H), 1.03 (s, 3H), 0.96 - 0.85 (m, 8H), 0.75 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 825.7 (M^++1).

Preparation of Compound 5104 and Compound 5105



Compound 5104



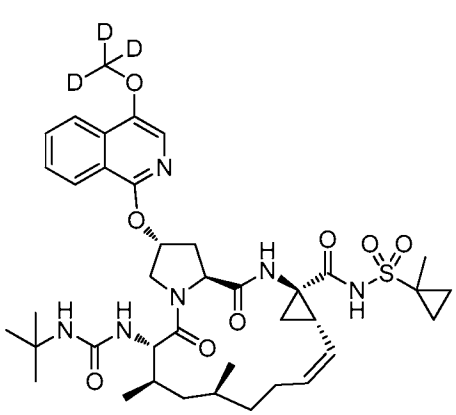
Compound 5105

Compound 5104 and Compound 5105 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

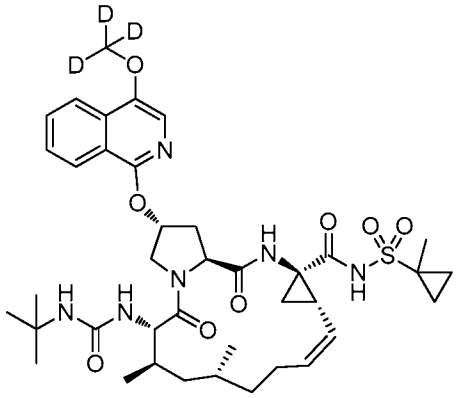
Compound 5104: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-(trideuteromethoxy)isoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 831.8 (M^++1).

Compound 5105: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-(trideuteromethoxy)isoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.14 (br. s., 1H), 8.07 (d, *J*=8.2 Hz, 1H), 8.10 (d, *J*=8.2 Hz, 1H), 7.87 - 7.75 (m, 2H), 7.68 - 7.58 (m, 2H), 5.78 (br. s., 1H), 5.53 (br. s., 1H), 4.97 (br. s., 1H), 4.64 - 4.41 (m, 2H), 3.96 - 3.88 (m, 1H), 3.70 (dd, *J*=10.7, 7.9 Hz, 1H), 2.69 (d, *J*=8.9 Hz, 1H), 2.62 (br. s., 1H), 2.39 - 2.25 (m, 2H), 1.95 - 1.80 (m, 2H), 1.70 (br. s., 1H), 1.62 (br. s., 1H), 1.52 (br. s., 1H), 1.41 (br. s., 5H), 1.35 (d, *J*=11.0 Hz, 1H), 1.29 (br. s., 1H), 1.15 (br. s., 1H), 0.97 - 0.86 (m, 8H), 0.75 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 831.8 (M^++1).

Preparation of Compound 5106 and Compound 5107



Compound 5106



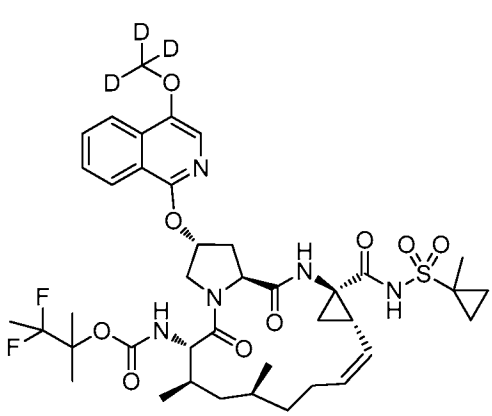
Compound 5107

Compound 5106 and Compound 5107 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

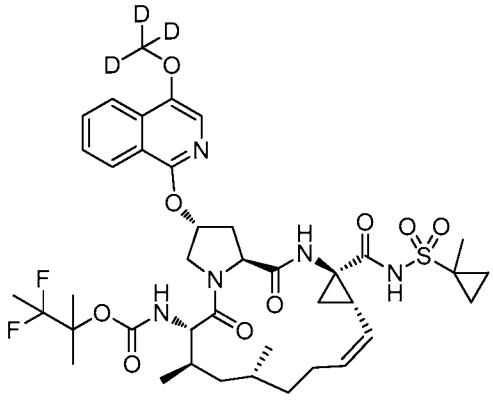
Compound 5106: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-2-((4-(trideuteromethoxy)isoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 770.7 (M^++1).

Compound 5107: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-2-((4-(trideuteromethoxy)isoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.07 (br. s., 1H), 8.12 (d, *J*=8.2 Hz, 1H), 8.06 (d, *J*=8.5 Hz, 1H), 7.79 (t, *J*=7.8 Hz, 1H), 7.64 (s, 1H), 7.58 (t, *J*=7.6 Hz, 1H), 5.94 (d, *J*=8.9 Hz, 1H), 5.78 (br. s., 1H), 5.56 (s, 1H), 5.52 (br. s., 1H), 4.97 (br. s., 1H), 4.58 (d, *J*=10.4 Hz, 1H), 4.49 - 4.37 (m, 1H), 3.98 - 3.82 (m, 2H), 2.75 (s, 1H), 2.59 (br. s., 1H), 2.38 - 2.23 (m, 2H), 1.94 - 1.85 (m, 1H), 1.69 (dd, *J*=17.2, 6.3 Hz, 2H), 1.60 (br. s., 1H), 1.41 (br. s., 6H), 1.36 (br. s., 1H), 1.28 (d, *J*=6.7 Hz, 1H), 1.15 (br. s., 1H), 1.02 (s, 9H), 0.92 (dd, *J*=16.6, 6.6 Hz, 8H), 0.74 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 770.7 (M^++1).

Preparation of Compound 5108 and Compound 5109



Compound 5108



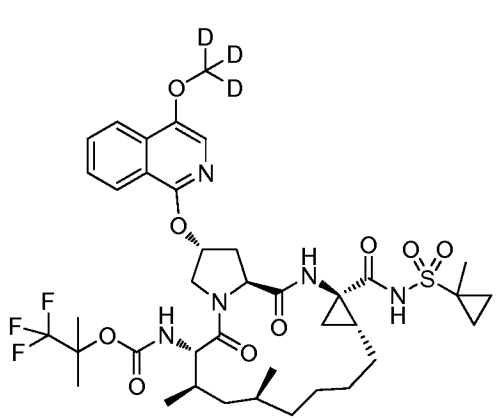
Compound 5109

Compound 5108 and Compound 5109 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

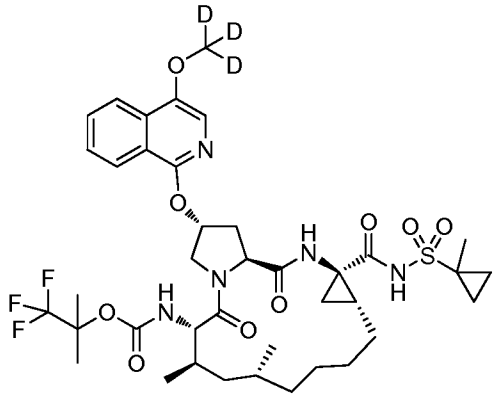
Compound 5108: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-(trideuteromethoxy)isoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 821.7 (M^++1).

Compound 5109: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-(trideuteromethoxy)isoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (br. s., 1H), 9.12 (br. s., 1H), 8.08 (m, 2H), 7.79 (t, *J*=7.6 Hz, 1H), 7.69 - 7.52 (m, 3H), 5.77 (br. s., 1H), 5.53 (m, 1H), 4.98 (m, 1H), 4.51 (m, 2H), 4.00 - 3.88 (m, 1H), 3.72 (dd, *J*=10.7, 8.5 Hz, 1H), 2.77 - 2.58 (m, 2H), 2.40 - 2.25 (m, 2H), 1.95 - 1.65 (m, 5H), 1.56 (t, *J*=19.7 Hz, 4H), 1.41 (m, 6H), 1.25 (s, 3H), 1.03 - 0.85 (m, 12H), 0.75 (m, 1H); MS: MS *m/z* 821.7 (M^++1).

Preparation of Compound 5110 and Compound 5111



Compound 5110



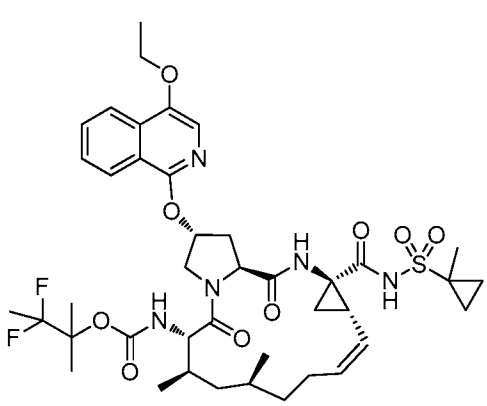
Compound 5111

Compound 5110 and Compound 5111 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 5117:

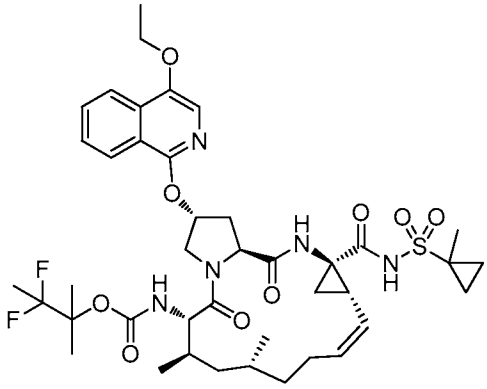
Compound 5110: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aR,14aR,16aS)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-(trideuteromethoxy)isoquinolin-1-yl)oxy)octadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 827.5 (M^++1).

Compound 5111: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aR,14aR,16aS)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-2-((4-(trideuteromethoxy)isoquinolin-1-yl)oxy)octadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.08 (br. s., 1H), 9.04 (br. s., 1H), 8.07 (d, *J*=8.5 Hz, 1H), 8.10 (d, *J*=8.2 Hz, 1H), 7.83 - 7.73 (m, 2H), 7.67 - 7.57 (m, 2H), 5.77 (br. s., 1H), 4.59 - 4.45 (m, 2H), 3.93 - 3.86 (m, 1H), 3.70 (dd, *J*=10.7, 8.2 Hz, 1H), 2.61 (br. s., 1H), 2.32 - 2.23 (m, 1H), 1.92 (s, 1H), 1.83 - 1.74 (m, 1H), 1.69 (d, *J*=13.1 Hz, 1H), 1.59 (d, *J*=10.4 Hz, 2H), 1.52 - 1.43 (m, 4H), 1.40 (d, *J*=6.1 Hz, 2H), 1.34 (s, 6H), 1.25 (br. s., 3H), 1.08 - 0.91 (m, 10H), 0.88 (d, *J*=6.4 Hz, 3H), 0.71 (t, *J*=11.4 Hz, 1H); MS: MS *m/z* 827.5 (M^++1).

Preparation of Compound 5112 and Compound 5113



Compound 5112



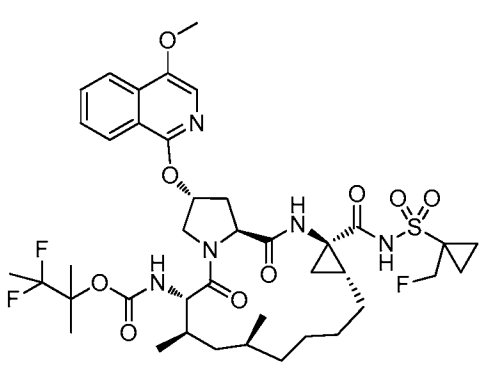
Compound 5113

Compound 5112 and Compound 5113 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

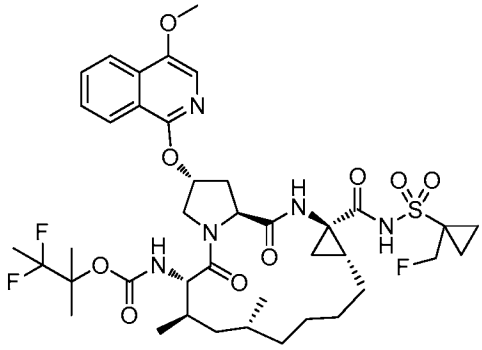
Compound 5112: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 832.4 (M^++1).

Compound 5113: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.11 (br. s., 1H), 8.08 (t, *J*=7.3 Hz, 2H), 7.79 (t, *J*=8.1 Hz, 1H), 7.67 - 7.58 (m, 3H), 5.78 (br. s., 1H), 5.53 (d, *J*=5.5 Hz, 1H), 4.98 (br. s., 1H), 4.62 - 4.44 (m, 2H), 4.21 (q, *J*=7.0 Hz, 2H), 3.98 - 3.84 (m, 1H), 3.72 (dd, *J*=10.7, 8.5 Hz, 1H), 2.77 - 2.68 (m, 1H), 2.68 - 2.58 (m, 1H), 2.40 - 2.23 (m, 2H), 1.98 - 1.79 (m, 2H), 1.69 (br. s., 1H), 1.56 (t, *J*=19.5 Hz, 5H), 1.49 - 1.39 (m, 8H), 1.36 (d, *J*=11.3 Hz, 1H), 1.32 - 1.23 (m, 4H), 1.15 (d, *J*=11.9 Hz, 1H), 1.01 - 0.84 (m, 11H), 0.76 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 832.5 (M^++1).

Preparation of Compound 5118 and Compound 5119



Compound 5118



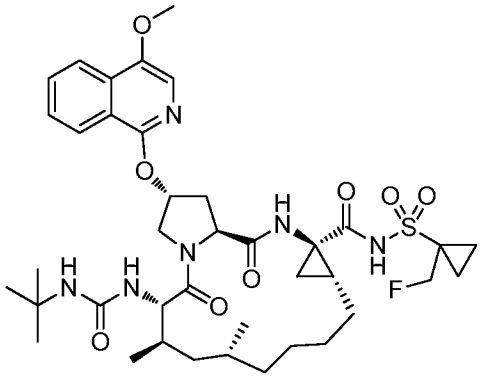
Compound 5119

Compound 5118 and Compound 5119 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 5117:

Compound 5118: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aR,14aR,16aS)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 838.4 (M^++1).

Compound 5119: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aR,14aR,16aS)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.39 (s, 1H), 8.97 (s, 1H), 8.07 (d, *J*=8.2 Hz, 1H), 8.10 (d, *J*=8.2 Hz, 1H), 7.79 (t, *J*=7.8 Hz, 1H), 7.66 (s, 1H), 7.64 - 7.53 (m, 2H), 5.77 (br. s., 1H), 4.86 - 4.69 (m, 1H), 4.68 - 4.45 (m, 3H), 3.98 (s, 3H), 3.95 - 3.86 (m, 1H), 3.71 (dd, *J*=10.5, 8.4 Hz, 1H), 2.60 (dd, *J*=13.4, 6.4 Hz, 1H), 2.34 - 2.21 (m, 1H), 1.92 (d, *J*=6.1 Hz, 1H), 1.83 - 1.73 (m, 1H), 1.69 (d, *J*=12.5 Hz, 1H), 1.57 (t, *J*=19.5 Hz, 7H), 1.40 - 1.21 (m, 12H), 1.06 - 0.92 (m, 8H), 0.89 (d, *J*=6.4 Hz, 3H), 0.72 (t, *J*=11.4 Hz, 1H); MS: MS *m/z* 838.4 (M^++1).

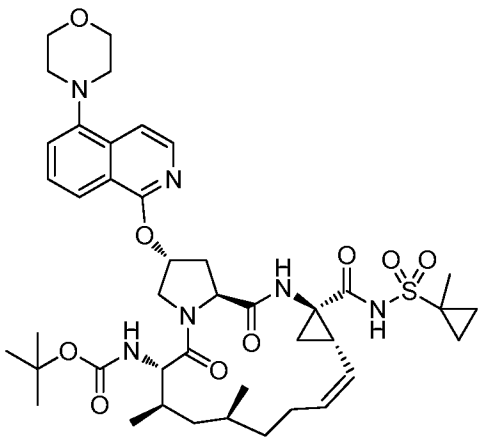
Preparation of Compound 5120



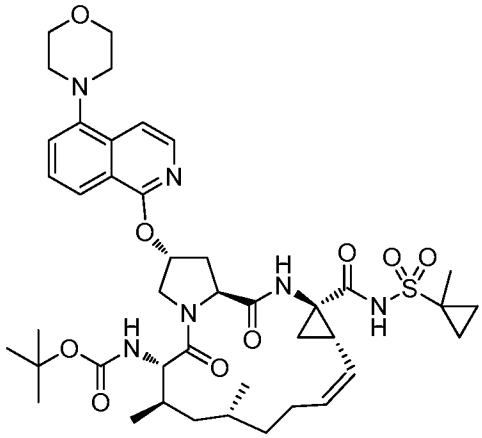
Compound 5120

Compound 5120 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 5117: Compound 5120: (2R,6S,7R,9R,13aR,14aR,16aS)-6-(3-(tert-butyl)ureido)-N-((1-(fluoromethyl)cyclopropyl)sulfonyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, METHANOL-d_4) δ ppm 8.17 (d, *J*=8.2 Hz, 1H), 8.09 (d, *J*=8.2 Hz, 1H), 7.74 - 7.67 (m, 1H), 7.55 (s, 1H), 7.54 - 7.49 (m, 1H), 5.85 - 5.74 (m, 1H), 4.81 - 4.64 (m, 2H), 4.64 - 4.50 (m, 2H), 4.08 - 4.03 (m, 2H), 4.01 (s, 3H), 2.73 (dd, *J*=13.9, 7.2 Hz, 1H), 2.41 (ddd, *J*=13.9, 9.9, 4.3 Hz, 1H), 1.86 (d, *J*=8.5 Hz, 1H), 1.77 - 1.55 (m, 6H), 1.49 - 1.37 (m, 2H), 1.36 - 1.15 (m, 6H), 1.15 - 1.06 (m, 10H), 1.04 - 0.90 (m, 7H), 0.81 - 0.68 (m, 2H); MS: MS *m/z* 787.4 (M^++1).

Preparation of Compound 5121 and Compound 5122



Compound 5121



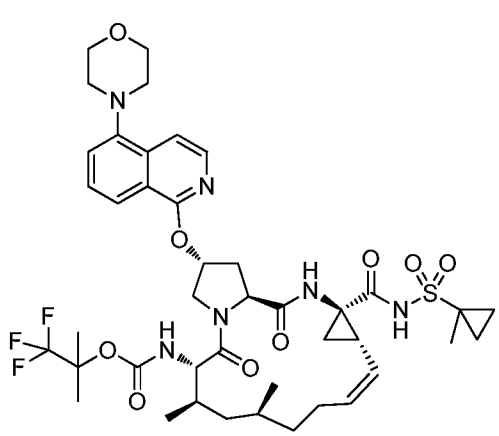
Compound 5122

Compound 5121 and Compound 5122 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

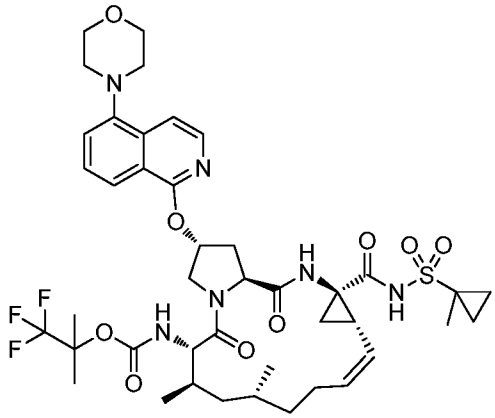
Compound 5121: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((5-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 823.4 (M^++1).

Compound 5122: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((5-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.10 (br. s., 1H), 8.03 (d, *J*=6.1 Hz, 1H), 7.86 (d, *J*=8.2 Hz, 1H), 7.59 - 7.50 (m, 1H), 7.46 (t, *J*=7.9 Hz, 1H), 7.35 (d, *J*=7.6 Hz, 1H), 7.17 (br. s., 1H), 5.83 (br. s., 1H), 5.51 (br. s., 1H), 4.98 (br. s., 1H), 4.61 (br. s., 1H), 4.47 (br. s., 1H), 3.97 - 3.82 (m, 5H), 3.76 - 3.65 (m, 1H), 3.09 - 2.92 (m, 4H), 2.60 (m, 2H), 2.35 - 2.23 (m, 2H), 1.94 - 1.85 (m, 1H), 1.81 (br. s., 1H), 1.71 (br. s., 1H), 1.59 (br. s., 1H), 1.40 (br. s., 6H), 1.24 (d, *J*=6.4 Hz, 2H), 1.11 (s, 10H), 1.04 (br. s., 1H), 0.96 - 0.84 (m, 7H), 0.72 (br. s., 1H); MS: MS *m/z* 823.4 (M^++1).

Preparation of Compound 5123 and Compound 5124



Compound 5123



Compound 5124

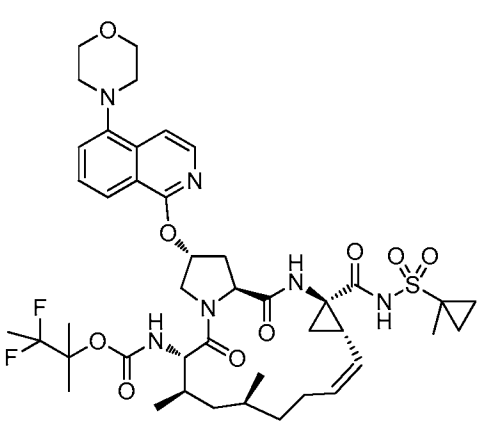
Compound 5123 and Compound 5124 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5123: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((5-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 877.4 (M^++1).

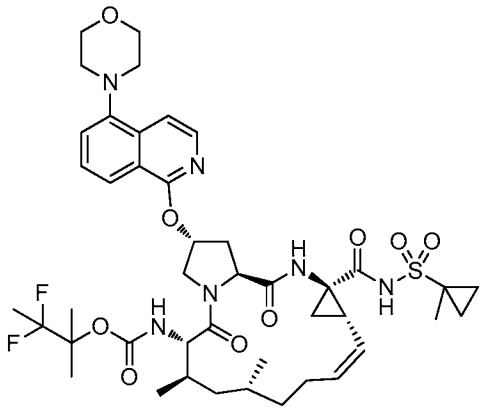
Compound 5124: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((5-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.14 (br. s., 1H), 8.04 (d, *J*=6.1 Hz, 1H), 7.84 (d, *J*=8.2 Hz, 2H), 7.59 - 7.46 (m, 2H), 7.36 (d, *J*=7.0 Hz, 1H), 5.84 (br. s., 1H), 5.52 (br. s., 1H), 4.98 (br. s., 1H), 4.63 - 4.43 (m, 2H), 3.98 - 3.83 (m, 5H), 3.70 (dd, *J*=10.7, 7.9 Hz, 1H), 3.08 - 2.95 (m, 4H), 2.72 - 2.58 (m, 2H), 2.39 - 2.24 (m, 2H), 1.94 - 1.79 (m, 2H), 1.70 (br. s., 1H), 1.61 (br. s., 1H), 1.50 (br. s.,

2H), 1.41 (br. s., 4H), 1.38 - 1.24 (m, 5H), 1.17 (d, *J*=13.1 Hz, 1H), 1.04 (s, 3H), 0.98 - 0.84 (m, 8H), 0.75 (br. s., 1H); MS: MS *m/z* 877.4 (M^++1).

Preparation of Compound 5125 and Compound 5126



Compound 5125



Compound 5126

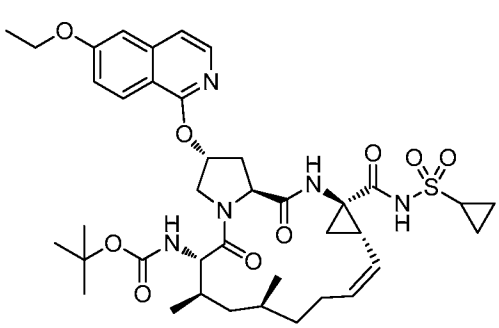
Compound 5125 and Compound 5126 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5125: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((5-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 873.4 (M^++1).

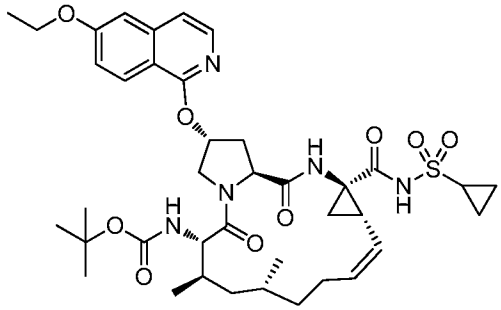
Compound 5126: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((5-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.11 (br. s., 1H), 8.04 (d, *J*=6.1 Hz, 1H), 7.84 (d, *J*=8.2 Hz, 1H), 7.62 (d, *J*=8.5 Hz, 1H), 7.54 (d, *J*=6.1 Hz, 1H), 7.48 (t, *J*=7.9 Hz, 1H), 7.36 (d, *J*=7.3 Hz, 1H), 5.84 (br. s., 1H), 5.53 (br. s., 1H), 4.98 (br. s., 1H), 4.58 (d, *J*=11.3 Hz, 1H), 4.52 (br. s., 1H), 3.97 - 3.82 (m, 5H), 3.72 (dd, *J*=10.7, 8.2 Hz, 1H), 3.08 - 2.94 (m, 4H), 2.78 - 2.68 (m, 1H), 2.65 (br. s., 1H),

2.42 - 2.26 (m, 2H), 1.94 - 1.87 (m, 1H), 1.83 (d, *J*=7.3 Hz, 1H), 1.69 (br. s., 1H), 1.57 (t, *J*=19.7 Hz, 5H), 1.41 (br. s., 5H), 1.37 (br. s., 1H), 1.29 (br. s., 1H), 1.24 (s, 3H), 1.14 (br. s., 1H), 1.00 - 0.85 (m, 11H), 0.81 - 0.70 (m, 1H); MS: MS *m/z* 873.4 (M^++1).

Preparation of Compound 5127 and Compound 5128



Compound 5127



Compound 5128

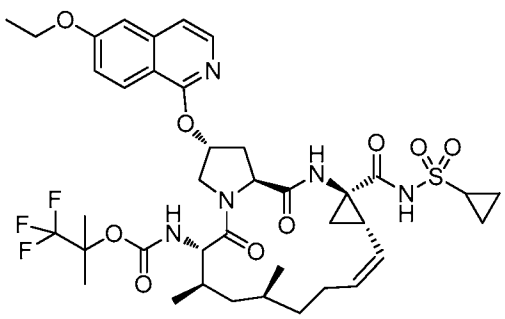
Compound 5127 and Compound 5128 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5127: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 768.4 (M^++1).

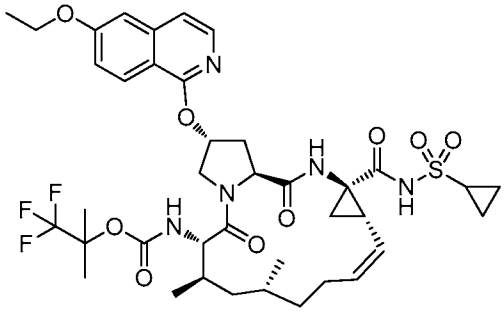
Compound 5128: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.18 (br. s., 1H), 8.97 (br. s., 1H), 8.04 (d, *J*=8.9 Hz, 1H), 7.98 - 7.90 (m, 1H), 7.35 - 7.27 (m, 2H), 7.19 (d, *J*=6.4 Hz, 1H), 7.09 (dd, *J*=9.2, 2.4 Hz, 1H), 5.80 (br. s., 1H), 5.52 (br. s., 1H), 5.05 (br. s., 1H), 4.57 (br. s., 1H), 4.43 (br. s., 1H), 4.18 (q, *J*=6.9 Hz, 2H), 3.95 - 3.82 (m, 1H), 3.77 - 3.67 (m, 1H), 2.67 (d, *J*=18.9 Hz, 1H), 2.61 (br. s., 1H), 2.36 - 2.23 (m, 2H), 1.91 (d, *J*=10.1 Hz, 1H), 1.82 (d, *J*=6.7 Hz, 1H), 1.72 (br. s., 1H), 1.59 (br. s., 1H), 1.53 (br. s., 1H),

1.47 - 1.34 (m, 6H), 1.18 - 1.06 (m, 12H), 1.03 - 0.84 (m, 8H), 0.72 (t, *J*=11.4 Hz, 1H); MS: MS *m/z* 768.4 (M^++1).

Preparation of Compound 5129 and Compound 5130



Compound 5129



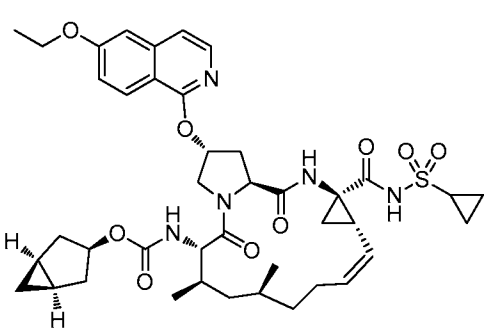
Compound 5130

Compound 5129 and Compound 5130 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

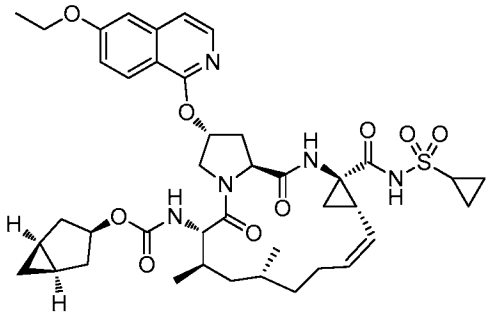
Compound 5129: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 822.3 (M^++1).

Compound 5130: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.19 (br. s., 1H), 9.01 (br. s., 1H), 8.01 (d, *J*=9.2 Hz, 1H), 7.96 (d, *J*=5.8 Hz, 1H), 7.83 (d, *J*=8.2 Hz, 1H), 7.37 - 7.27 (m, 2H), 7.14 (dd, *J*=9.2, 2.4 Hz, 1H), 5.81 (br. s., 1H), 5.52 (br. s., 1H), 5.05 (br. s., 1H), 4.59 - 4.43 (m, 2H), 4.18 (q, *J*=6.9 Hz, 2H), 3.95 - 3.83 (m, 1H), 3.71 (dd, *J*=10.8, 8.1 Hz, 1H), 2.71 - 2.57 (m, 2H), 2.36 - 2.23 (m, 2H), 1.94 - 1.76 (m, 2H), 1.71 (br. s., 1H), 1.61 - 1.13 (m, 16H), 1.04 - 0.84 (m, 9H), 0.74 (t, *J*=13.0 Hz, 1H); MS: MS *m/z* 822.3 (M^++1).

Preparation of Compound 5131 and Compound 5132



Compound 5131



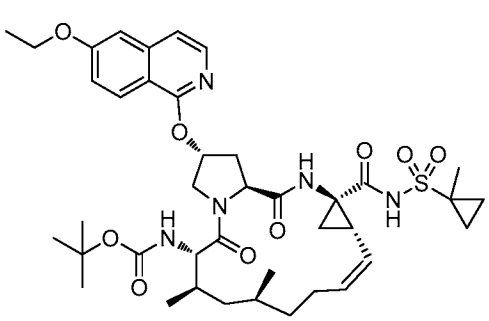
Compound 5132

Compound 5131 and Compound 5132 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

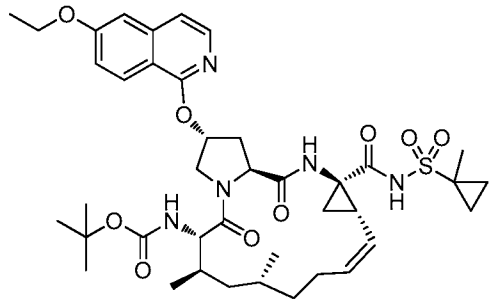
Compound 5131: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 792.4 (M^++1).

Compound 5132: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.19 (br. s., 1H), 8.94 (br. s., 1H), 8.02 (d, *J*=8.9 Hz, 1H), 7.98 - 7.91 (m, 1H), 7.40 (d, *J*=8.2 Hz, 1H), 7.35 - 7.27 (m, 2H), 7.16 (dd, *J*=9.2, 2.4 Hz, 1H), 5.82 (br. s., 1H), 5.52 (br. s., 1H), 5.07 (br. s., 1H), 4.67 (t, *J*=6.7 Hz, 1H), 4.55 - 4.37 (m, 2H), 4.18 (q, *J*=7.0 Hz, 2H), 3.96 - 3.86 (m, 1H), 3.81 - 3.70 (m, 1H), 2.61 (m, 2H), 2.35 - 2.22 (m, 2H), 2.02 - 1.90 (m, 2H), 1.88 - 1.76 (m, 2H), 1.67 (br. s., 1H), 1.62 - 1.51 (m, 3H), 1.48 - 1.31 (m, 7H), 1.26 - 1.06 (m, 5H), 0.93 (d, *J*=7.0 Hz, 5H), 0.87 (d, *J*=6.4 Hz, 3H), 0.72 (t, *J*=13.0 Hz, 1H), 0.40 - 0.32 (m, 2H); MS: MS *m/z* 792.4 (M^++1).

Preparation of Compound 5133 and Compound 5134



Compound 5133



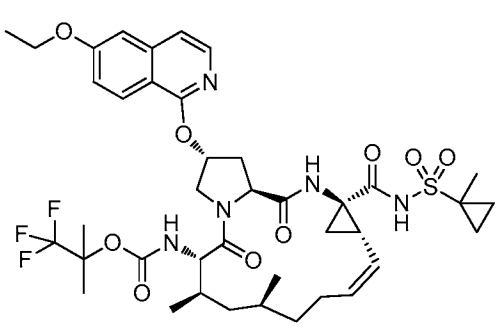
Compound 5134

Compound 5133 and Compound 5134 were were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

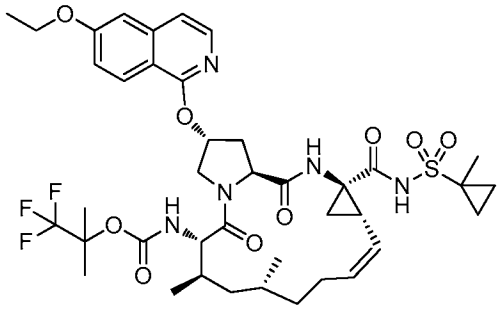
Compound 5133: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 782.4 (M^++1).

Compound 5134: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.04 (br. s., 1H), 9.09 (br. s., 1H), 8.04 (d, *J*=9.2 Hz, 1H), 7.97 - 7.91 (m, 1H), 7.34 - 7.25 (m, 2H), 7.19 (d, *J*=7.3 Hz, 1H), 7.10 (dd, *J*=9.2, 2.4 Hz, 1H), 5.82 (br. s., 1H), 5.52 (br. s., 1H), 4.97 (br. s., 1H), 4.59 (d, *J*=9.2 Hz, 1H), 4.47 (br. s., 1H), 4.18 (q, *J*=6.9 Hz, 2H), 3.95 - 3.88 (m, 1H), 3.73 (dd, *J*=10.4, 8.5 Hz, 1H), 2.71 (s, 1H), 2.59 (br. s., 1H), 2.39 - 2.25 (m, 2H), 1.94 - 1.77 (m, 2H), 1.70 - 1.23 (m, 13H), 1.17 - 1.06 (m, 10H), 0.98 - 0.82 (m, 8H), 0.73 (t, *J*=11.7 Hz, 1H); MS: MS *m/z* 782.4 (M^++1).

Preparation of Compound 5135 and Compound 5136



Compound 5135



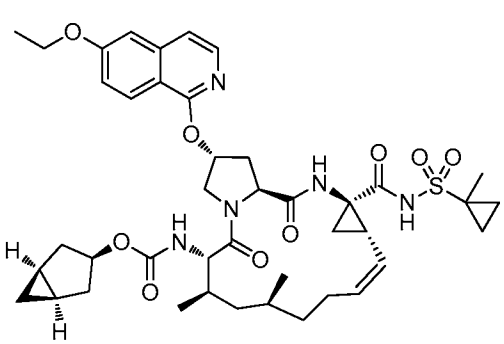
Compound 5136

Compound 5135 and Compound 5136 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

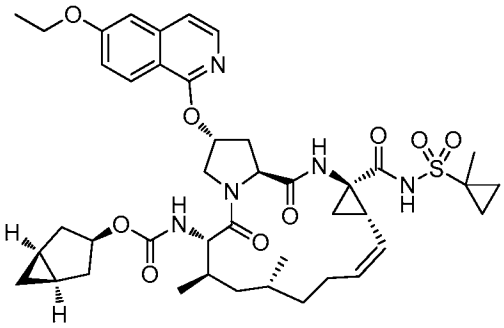
Compound 5135: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 836.3 (M^++1).

Compound 5136: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.04 (br. s., 1H), 9.13 (br. s., 1H), 8.01 (d, *J*=9.2 Hz, 1H), 7.96 (d, *J*=6.1 Hz, 1H), 7.84 (d, *J*=7.9 Hz, 1H), 7.34 - 7.28 (m, 2H), 7.14 (dd, *J*=9.0, 2.3 Hz, 1H), 5.82 (br. s., 1H), 5.53 (br. s., 1H), 4.98 (br. s., 1H), 4.53 (br. s., 2H), 4.18 (q, *J*=6.8 Hz, 2H), 3.96 - 3.86 (m, 1H), 3.71 (dd, *J*=10.7, 7.9 Hz, 1H), 2.73 (d, *J*=18.0 Hz, 1H), 2.61 (br. s., 1H), 2.41 - 2.22 (m, 2H), 1.94 - 1.81 (m, 2H), 1.70 (br. s., 1H), 1.61 (br. s., 1H), 1.51 (br. s., 1H), 1.48 - 1.32 (m, 12H), 1.27 (d, *J*=17.7 Hz, 1H), 1.15 (br. s., 1H), 1.11 (s, 3H), 0.98 - 0.82 (m, 8H), 0.75 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 836.3 (M^++1).

Preparation of Compound 5137 and Compound 5138



Compound 5137



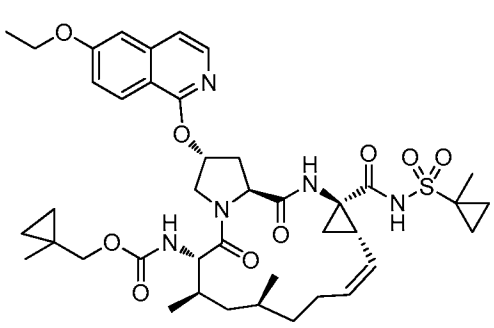
Compound 5138

Compound 5137 and Compound 5138 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

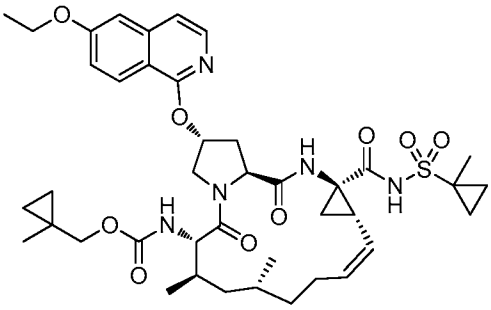
Compound 5137: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 806.4 (M^++1).

Compound 5138: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.04 (br. s., 1H), 9.06 (br. s., 1H), 8.02 (d, *J*=9.2 Hz, 1H), 7.98 - 7.89 (m, 1H), 7.40 (d, *J*=7.9 Hz, 1H), 7.35 - 7.27 (m, 2H), 7.16 (dd, *J*=9.0, 2.3 Hz, 1H), 5.83 (br. s., 1H), 5.51 (br. s., 1H), 4.99 (br. s., 1H), 4.65 (t, *J*=6.7 Hz, 1H), 4.47 (br. s., 2H), 4.18 (q, *J*=7.0 Hz, 2H), 3.99 - 3.88 (m, 1H), 3.76 (dd, *J*=10.5, 9.0 Hz, 1H), 2.76 - 2.68 (m, 1H), 2.59 (br. s., 1H), 2.37 - 2.24 (m, 2H), 2.02 - 1.89 (m, 2H), 1.87 - 1.74 (m, 2H), 1.67 - 1.07 (m, 18H), 0.93 - 0.73 (m, 9H), 0.40 - 0.29 (m, 2H); MS: MS *m/z* 806.4 (M^++1).

Preparation of Compound 5139 and Compound 5140



Compound 5139



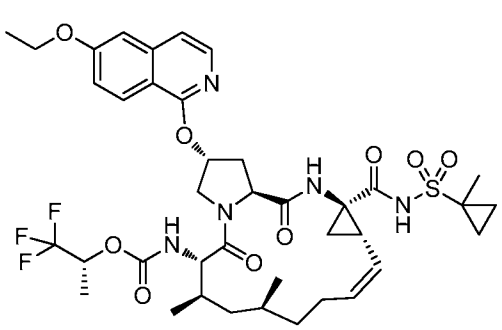
Compound 5140

Compound 5139 and Compound 5140 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

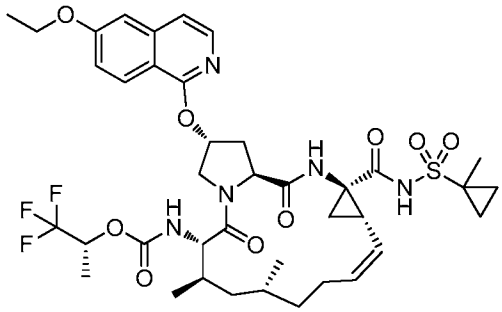
Compound 5139: (1-methylcyclopropyl)methyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 794.4 (M^++1).

Compound 5140: (1-methylcyclopropyl)methyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 8.01 (d, *J*=9.2 Hz, 1H), 7.98 - 7.87 (m, 1H), 7.47 (d, *J*=6.7 Hz, 1H), 7.36 - 7.26 (m, 2H), 7.13 (dd, *J*=8.9, 2.4 Hz, 1H), 5.82 (br. s., 1H), 5.43 (br. s., 1H), 4.44 (br. s., 2H), 4.24 - 4.07 (m, 2H), 3.99 - 3.86 (m, 1H), 3.82 - 3.65 (m, 1H), 3.48 - 3.38 (m, 2H), 2.36 - 2.25 (m, 2H), 1.95 - 1.86 (m, 1H), 1.83 (d, *J*=5.2 Hz, 1H), 1.75 (br. s., 1H), 1.49 (br. s., 1H), 1.46 - 1.31 (m, 10H), 1.25 (br. s., 2H), 1.20 (br. s., 2H), 0.97 - 0.84 (m, 10H), 0.80 (br. s., 1H), 0.70 (br. s., 2H), 0.32 - 0.09 (m, 4H); MS: MS *m/z* 794.4 (M^++1).

Preparation of Compound 5141 and Compound 5142



Compound 5141



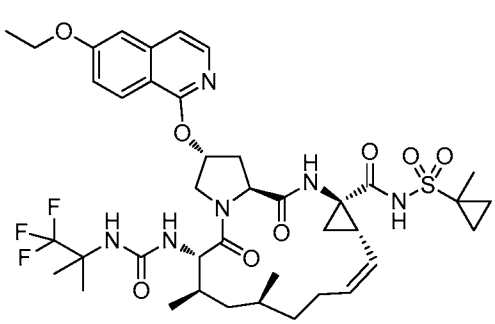
Compound 5142

Compound 5141 and Compound 5142 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

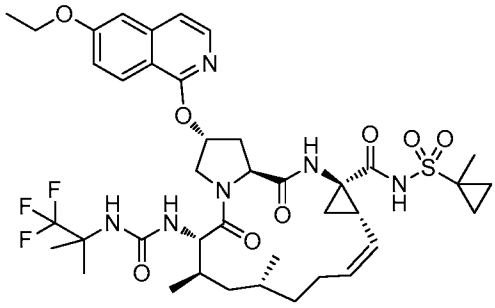
Compound 5141: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 822.3 (M^++1).

Compound 5142: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.03 (br. s., 1H), 9.10 (br. s., 1H), 8.08 (d, *J*=8.2 Hz, 1H), 8.00 - 7.91 (m, 2H), 7.33 - 7.28 (m, 2H), 7.08 (dd, *J*=9.2, 2.4 Hz, 1H), 5.83 (br. s., 1H), 5.52 (br. s., 1H), 4.98 (br. s., 1H), 4.73 (dt, *J*=13.6, 6.6 Hz, 1H), 4.59 - 4.39 (m, 2H), 4.22 - 4.10 (m, 2H), 3.99 - 3.89 (m, 1H), 3.78 (dd, *J*=10.7, 8.2 Hz, 1H), 2.75 - 2.63 (m, 1H), 2.61 (br. s., 1H), 2.35 - 2.19 (m, 2H), 1.98 - 1.80 (m, 2H), 1.70 (br. s., 1H), 1.60 (br. s., 1H), 1.52 (br. s., 1H), 1.47 - 1.31 (m, 9H), 1.31 - 1.24 (m, 1H), 1.23 - 1.08 (m, 4H), 1.00 - 0.82 (m, 8H), 0.81 - 0.66 (m, 1H); MS: MS *m/z* 822.3 (M^++1).

Preparation of Compound 5143 and Compound 5144



Compound 5143



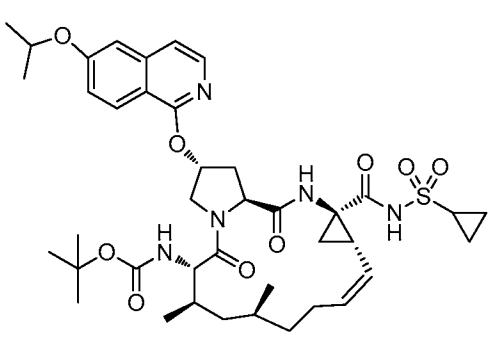
Compound 5144

Compound 5143 and Compound 5144 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

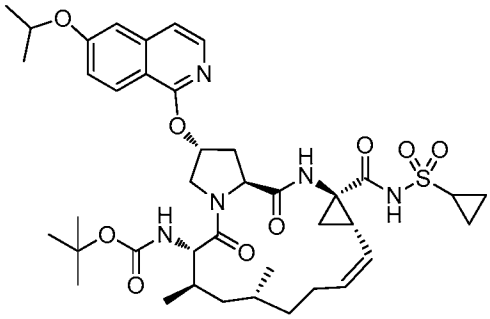
Compound 5143: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-6-(3-(1,1,1-trifluoro-2-methylpropan-2-yl)ureido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 835.4 (M^++1).

Compound 5144: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-6-(3-(1,1,1-trifluoro-2-methylpropan-2-yl)ureido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 8.13 (s, 1H), 8.02 (d, *J*=9.2 Hz, 1H), 7.95 (d, *J*=6.1 Hz, 1H), 7.32 - 7.26 (m, 2H), 7.10 (dd, *J*=8.9, 2.4 Hz, 1H), 6.20 (d, *J*=8.9 Hz, 1H), 6.15 (s, 1H), 5.78 (br. s., 1H), 5.66 (t, *J*=10.2 Hz, 1H), 5.31 (td, *J*=10.1, 6.0 Hz, 1H), 4.39 - 4.27 (m, 2H), 4.18 (q, *J*=6.9 Hz, 2H), 4.00 - 3.80 (m, 3H), 2.46 - 2.10 (m, 2H), 1.84 (d, *J*=13.7 Hz, 3H), 1.63 (d, *J*=6.7 Hz, 1H), 1.46 - 1.16 (m, 17H), 1.07 (s, 2H), 0.97 - 0.84 (m, 6H), 0.65 (t, *J*=10.2 Hz, 1H), 0.46 - 0.30 (m, 2H); MS: MS *m/z* 835.4 (M^++1).

Preparation of Compound 5145 and Compound 5146



Compound 5145



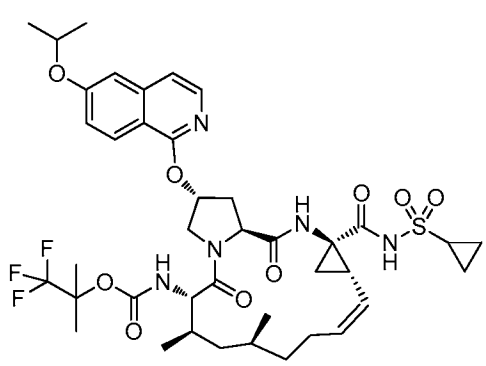
Compound 5146

Compound 5145 and Compound 5146 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

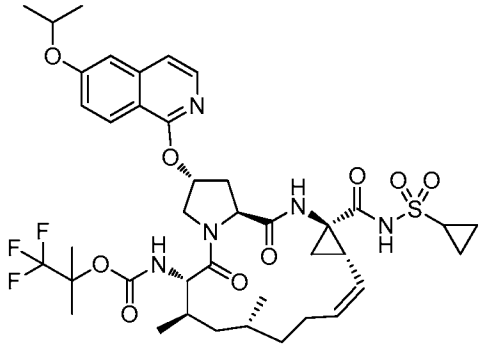
Compound 5145: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 782.4 (M^++1).

Compound 5146: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.19 (br. s., 1H), 8.98 (br. s., 1H), 8.03 (d, *J*=8.9 Hz, 1H), 7.94 (d, *J*=5.8 Hz, 1H), 7.37 - 7.25 (m, 2H), 7.18 (d, *J*=5.8 Hz, 1H), 7.06 (dd, *J*=9.2, 2.4 Hz, 1H), 5.80 (br. s., 1H), 5.52 (br. s., 1H), 5.05 (br. s., 1H), 4.81 (dt, *J*=12.1, 6.0 Hz, 1H), 4.58 (d, *J*=8.9 Hz, 1H), 4.44 (br. s., 1H), 3.94 - 3.82 (m, 1H), 3.79 - 3.64 (m, 1H), 2.91 (s, 1H), 2.70 (br. s., 1H), 2.61 (br. s., 1H), 2.36 - 2.17 (m, 2H), 1.96 - 1.71 (m, 3H), 1.60 (br. s., 1H), 1.54 (br. s., 1H), 1.42 (br. s., 1H), 1.35 (dd, *J*=6.0, 2.9 Hz, 7H), 1.16 - 0.85 (m, 20H), 0.76 - 0.67 (m, 1H); MS: MS *m/z* 782.4 (M^++1).

Preparation of Compound 5147 and Compound 5148



Compound 5147



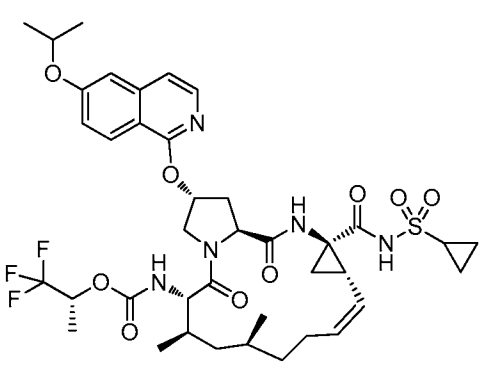
Compound 5148

Compound 5147 and Compound 5148 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

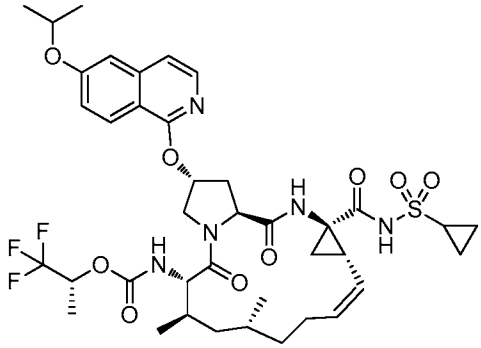
Compound 5147: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 836.3 (M^++1).

Compound 5148: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.20 (br. s., 1H), 9.03 (br. s., 1H), 8.03 - 7.91 (m, 2H), 7.81 (d, *J*=6.7 Hz, 1H), 7.35 - 7.26 (m, 2H), 7.11 (dd, *J*=9.2, 2.4 Hz, 1H), 5.81 (br. s., 1H), 5.52 (br. s., 1H), 5.05 (br. s., 1H), 4.82 (dt, *J*=12.0, 6.1 Hz, 1H), 4.50 (d, *J*=8.9 Hz, 2H), 3.94 - 3.78 (m, 1H), 3.69 (dd, *J*=10.5, 8.1 Hz, 1H), 2.90 (br. s., 1H), 2.66 (d, *J*=10.1 Hz, 1H), 2.61 (br. s., 1H), 2.36 - 2.28 (m, 2H), 1.95 - 1.78 (m, 2H), 1.70 (br. s., 1H), 1.60 (br. s., 1H), 1.56 (br. s., 1H), 1.42 (br. s., 1H), 1.39 - 1.27 (m, 11H), 1.13 (br. s., 2H), 1.04 (s, 4H), 0.93 (d, *J*=6.7 Hz, 4H), 0.88 (d, *J*=6.1 Hz, 3H), 0.73 (br. s., 1H); MS: MS *m/z* 836.3 (M^++1).

Preparation of Compound 5149 and Compound 5150



Compound 5149



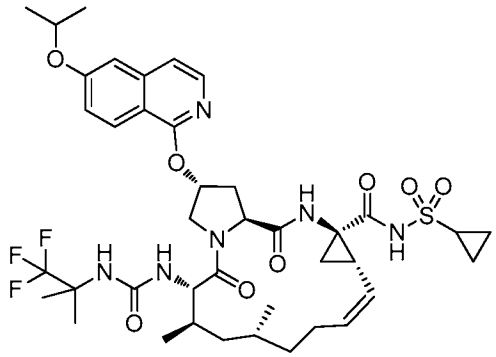
Compound 5150

Compound 5149 and Compound 5150 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5149: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 822.3 (M^++1).

Compound 5150: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.17 (s, 1H), 8.97 (br. s., 1H), 8.08 (d, *J*=7.9 Hz, 1H), 8.00 - 7.91 (m, 2H), 7.35 - 7.26 (m, 2H), 7.05 (dd, *J*=9.2, 2.1 Hz, 1H), 5.82 (br. s., 1H), 5.52 (br. s., 1H), 5.06 (t, *J*=8.9 Hz, 1H), 4.86 - 4.72 (m, 2H), 4.55 - 4.40 (m, 2H), 3.96 - 3.88 (m, 1H), 3.78 (dd, *J*=10.4, 8.2 Hz, 1H), 2.98 - 2.87 (m, 1H), 2.73 - 2.55 (m, 2H), 2.35 - 2.21 (m, 2H), 1.97 - 1.82 (m, 2H), 1.70 - 1.55 (m, 3H), 1.44 - 1.35 (m, 8H), 1.20 (d, *J*=6.7 Hz, 4H), 1.11 (d, *J*=6.1 Hz, 2H), 1.01 - 0.86 (m, 8H), 0.82 - 0.70 (m, 1H); MS: MS *m/z* 822.3 (M^++1).

Preparation of Compound 5151

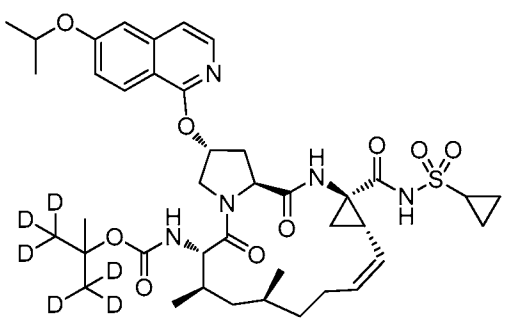


Compound 5151

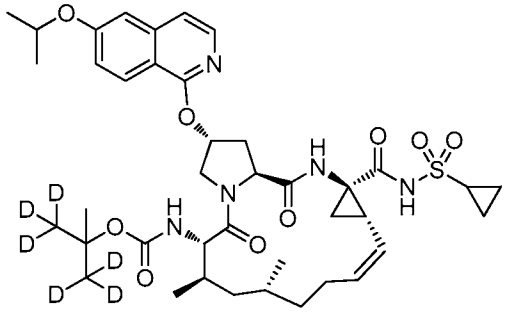
Compound 5151 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5151: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.17 (br. s., 1H), 8.96 (br. s., 1H), 8.05 - 7.90 (m, 2H), 7.33 - 7.25 (m, 2H), 7.06 (dd, *J*=9.2, 2.4 Hz, 1H), 6.23 (d, *J*=6.4 Hz, 1H), 6.08 (s, 1H), 5.81 (br. s., 1H), 5.51 (br. s., 1H), 5.06 (br. s., 1H), 4.88 - 4.69 (m, 1H), 4.48 (br. s., 1H), 4.41 (br. s., 1H), 3.97 - 3.78 (m, 2H), 2.91 (s, 1H), 2.61 (m, 2H), 2.35 - 2.25 (m, 2H), 1.91 - 1.35 (m, 13H), 1.23 - 1.10 (m, 9H), 0.92 (dd, *J*=17.2, 6.6 Hz, 8H), 0.74 (br. s., 1H); MS: MS *m/z* 835.4 (M^++1).

Preparation of Compound 5152 and Compound 5153



Compound 5152



Compound 5153

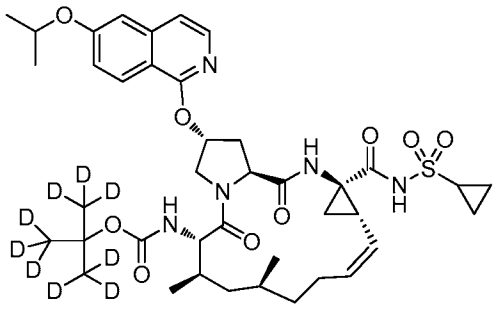
Compound 5152 and Compound 5153 were prepared using the intermediates

described herein and by following the general procedure described for the synthesis of Compound 3117:

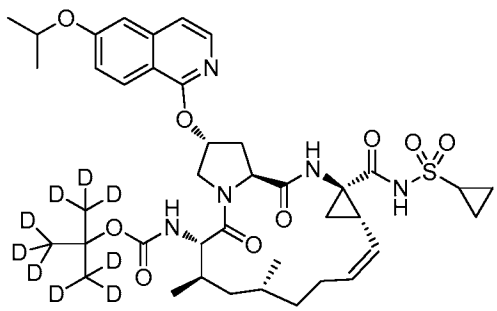
Compound 5152: 1,1,1,3,3,3-hexadeutero-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 788.8 (M^++1).

Compound 5153: 1,1,1,3,3,3-hexadeutero-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate.^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.18 (br. s., 1H), 8.97 (br. s., 1H), 8.03 (d, *J*=9.2 Hz, 1H), 7.93 (d, *J*=5.8 Hz, 1H), 7.36 - 7.24 (m, 2H), 7.16 (br. s., 1H), 7.06 (dd, *J*=9.0, 2.3 Hz, 1H), 5.80 (br. s., 1H), 5.51 (br. s., 1H), 5.05 (br. s., 1H), 4.81 (dt, *J*=12.0, 6.1 Hz, 1H), 4.56 (br. s., 1H), 4.43 (br. s., 1H), 3.94 - 3.82 (m, 1H), 3.79 - 3.60 (m, 1H), 2.91 (s, 1H), 2.67 (d, *J*=16.5 Hz, 1H), 2.59 (br. s., 1H), 2.35 - 2.21 (m, 2H), 1.97 - 1.86 (m, 1H), 1.82 (d, *J*=6.1 Hz, 1H), 1.72 (br. s., 1H), 1.59 - 1.35 (m, 10H), 1.21 - 1.08 (m, 5H), 1.05 (br. s., 1H), 1.01 - 0.85 (m, 8H), 0.71 (br. s., 1H); MS: MS *m/z* 788.7 (M^++1).

Preparation of Compound 5154 and Compound 5155



Compound 5154



Compound 5155

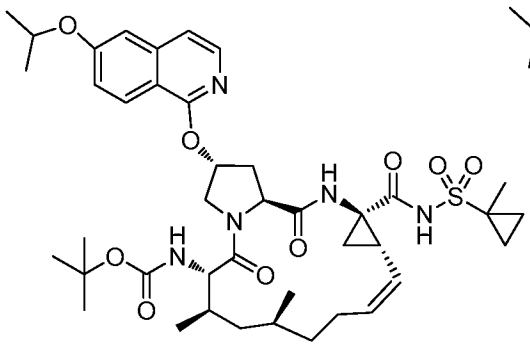
Compounds 5154 and 5155 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5154: 1,1,1,3,3,3-hexadeutero-2-(trideuteromethyl)propan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-

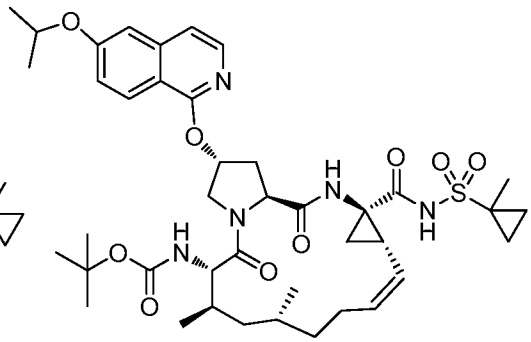
isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 791.8 (M^++1).

Compound 5155: 1,1,1,3,3,3-hexadeutero-2-(trideuteromethyl)propan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.18 (br. s., 1H), 8.97 (br. s., 1H), 8.03 (d, *J*=9.2 Hz, 1H), 7.94 (d, *J*=6.1 Hz, 1H), 7.35 - 7.26 (m, 2H), 7.15 (br. s., 1H), 7.06 (dd, *J*=9.2, 2.4 Hz, 1H), 5.80 (br. s., 1H), 5.52 (br. s., 1H), 5.06 (br. s., 1H), 4.81 (dt, *J*=12.1, 6.0 Hz, 1H), 4.56 (br. s., 1H), 4.43 (br. s., 1H), 3.96 - 3.83 (m, 1H), 3.76 - 3.60 (m, 1H), 2.91 (s, 1H), 2.67 (d, *J*=19.8 Hz, 1H), 2.59 (br. s., 1H), 2.34 - 2.25 (m, 2H), 1.96 - 1.86 (m, 1H), 1.82 (d, *J*=6.1 Hz, 1H), 1.72 (br. s., 1H), 1.59 (br. s., 2H), 1.42 (br. s., 1H), 1.35 (dd, *J*=6.0, 2.9 Hz, 8H), 1.11 (br. s., 2H), 1.02 - 0.85 (m, 8H), 0.71 (br. s., 1H); MS: MS *m/z* 791.8 (M^++1).

Preparation of Compound 5156 and Compound 5157



Compound 5156



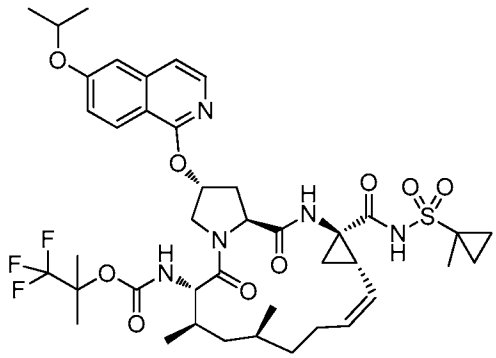
Compound 5157

Compounds 5156 and 5157 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

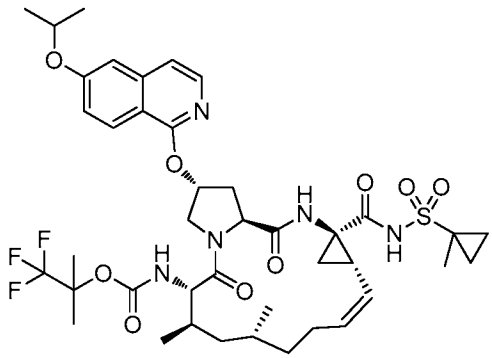
Compound 5156: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 796.7 (M^++1).

Compound 5157: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.10 (br. s., 1H), 8.03 (d, *J*=9.2 Hz, 1H), 7.93 (d, *J*=5.8 Hz, 1H), 7.32 - 7.26 (m, 2H), 7.17 (d, *J*=7.9 Hz, 1H), 7.07 (dd, *J*=9.0, 2.3 Hz, 1H), 5.82 (br. s., 1H), 5.58 - 5.47 (m, 1H), 4.93-5.01 (m,1H), 4.81 (quin, *J*=6.0 Hz, 1H), 4.58 (d, *J*=10.7 Hz, 1H), 4.48 (br. s., 1H), 3.95 - 3.88 (m, 1H), 3.77 - 3.67 (m, 1H), 2.76 - 2.55 (m, 2H), 2.40 - 2.24 (m, 2H), 1.95 - 0.66 (m, 37H); MS: MS *m/z* 796.7 (M^++1).

Preparation of Compound 5158 and Compound 5159



Compound 5158



Compound 5159

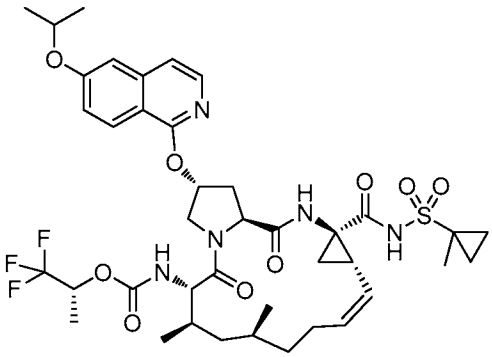
Compounds 5158 and 5159 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5158: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 850.4 (M^++1).

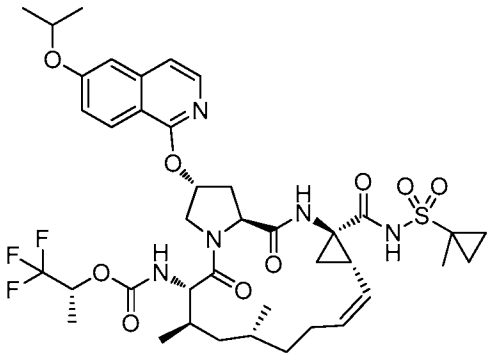
Compound 5159: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-

a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.15 (br. s., 1H), 8.06 - 7.90 (m, 2H), 7.81 (d, *J*=7.9 Hz, 1H), 7.36 - 7.23 (m, 2H), 7.11 (dd, *J*=9.2, 2.1 Hz, 1H), 5.82 (br. s., 1H), 5.53 (br. s., 1H), 4.97 (br. s., 1H), 4.82 (dt, *J*=12.0, 6.1 Hz, 1H), 4.53 (br. s., 2H), 3.96 - 3.85 (m, 1H), 3.69 (dd, *J*=10.7, 8.2 Hz, 1H), 2.72 - 2.63 (m, 1H), 2.61 (br. s., 1H), 2.41 - 2.19 (m, 2H), 1.91 (d, *J*=15.9 Hz, 1H), 1.84 (d, *J*=6.1 Hz, 1H), 1.69 (br. s., 1H), 1.62 (br. s., 1H), 1.51 (br. s., 1H), 1.41 - 1.15 (m, 17H), 1.01 (s, 3H), 0.96 - 0.84 (m, 8H), 0.75 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 850.4 (M^++1).

Preparation of Compound 5160 and Compound 5161



Compound 5160



Compound 5161

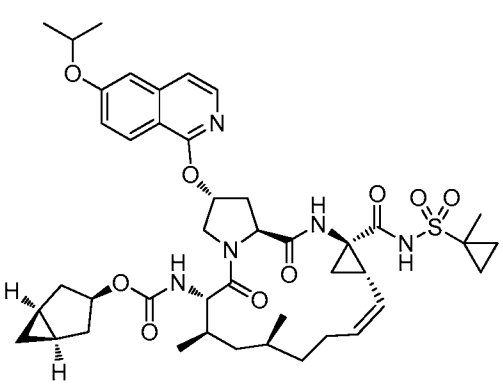
Compounds 5160 and 5161 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5160: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 836.3 (M^++1).

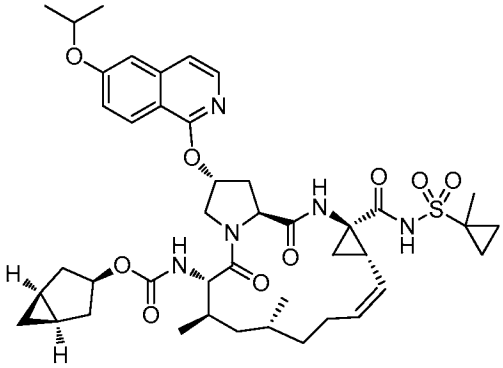
Compound 5161: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm

11.03 (s, 1H), 9.10 (br. s., 1H), 8.07 (d, *J*=7.6 Hz, 1H), 8.01 - 7.84 (m, 2H), 7.35 - 7.22 (m, 2H), 7.05 (dd, *J*=9.2, 2.4 Hz, 1H), 5.84 (br. s., 1H), 5.53 (d, *J*=5.2 Hz, 1H), 4.98 (t, *J*=9.3 Hz, 1H), 4.86 - 4.68 (m, 2H), 4.57 - 4.39 (m, 2H), 4.00 - 3.83 (m, 1H), 3.78 (dd, *J*=10.7, 8.2 Hz, 1H), 2.72 - 2.63 (m, 1H), 2.60 (br. s., 1H), 2.35 - 2.22 (m, 2H), 2.00 - 1.81 (m, 2H), 1.69 - 1.25 (m, 16H), 1.21 - 1.12 (m, 4H), 0.92 (dd, *J*=15.3, 6.7 Hz, 8H), 0.80 - 0.69 (m, 1H); MS: MS *m/z* 836.3 (M^++1).

Preparation of Compound 5162 and Compound 5163



Compound 5162



Compound 5163

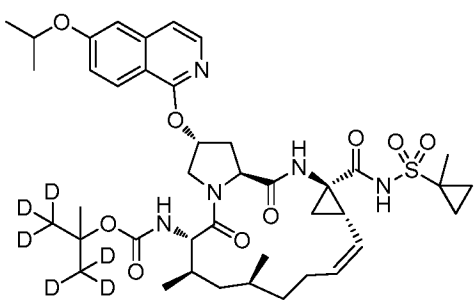
Compounds 5162 and 5163 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5162: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 820.4 (M^++1).

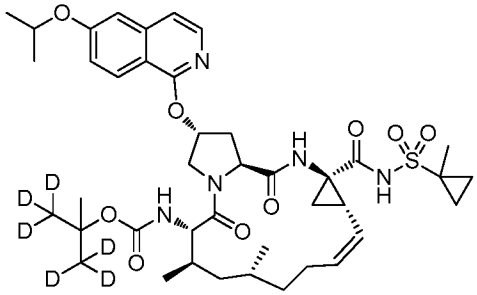
Compound 5163: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.08 (br. s., 1H), 8.00 (d, *J*=8.9 Hz, 1H), 7.93 (d, *J*=6.1 Hz, 1H), 7.38 (d, *J*=8.5 Hz, 1H), 7.35 - 7.26 (m, 2H), 7.13 (dd, *J*=9.0, 2.3 Hz, 1H), 5.84 (br. s.,

1H), 5.53 (br. s., 1H), 4.98 (br. s., 1H), 4.82 (dt, *J*=12.1, 5.9 Hz, 1H), 4.59 (t, *J*=6.7 Hz, 1H), 4.48 (d, *J*=9.8 Hz, 2H), 3.96 - 3.86 (m, 1H), 3.78 - 3.67 (m, 1H), 2.73 (d, *J*=16.8 Hz, 1H), 2.60 (br. s., 1H), 2.41 - 2.22 (m, 2H), 1.97 - 1.87 (m, 2H), 1.83 (d, *J*=6.4 Hz, 1H), 1.80 - 1.28 (m, 19H), 1.22 - 1.15 (m, 1H), 1.15 - 1.06 (m, 2H), 0.99 - 0.82 (m, 8H), 0.73 (t, *J*=12.4 Hz, 1H), 0.38 - 0.27 (m, 2H); MS: MS *m/z* 820.4 (M^++1).

Preparation of Compound 5164 and Compound 5165



Compound 5164



Compound 5165

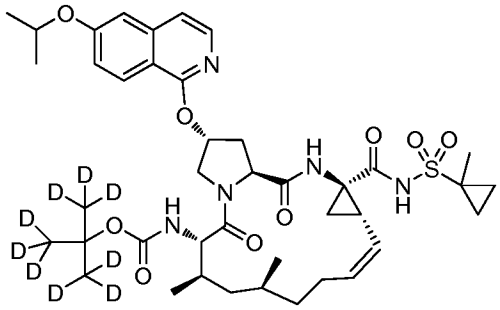
Compounds 5164 and 5165 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5164: 1,1,1,3,3,3-hexachloro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 802.7 (M^++1).

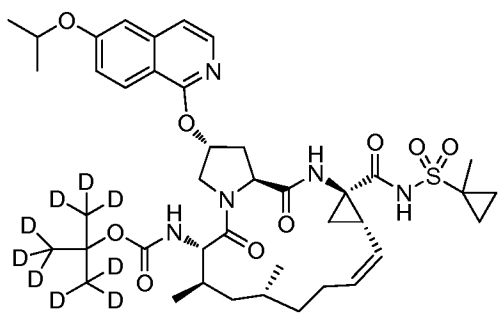
Compound 5165: 1,1,1,3,3,3-hexachloro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.10 (br. s., 1H), 8.03 (d, *J*=9.2 Hz, 1H), 7.93 (d, *J*=6.1 Hz, 1H), 7.35 - 7.24 (m, 2H), 7.17 (d, *J*=7.6 Hz, 1H), 7.07 (dd, *J*=9.0, 2.3 Hz, 1H), 5.82 (br. s., 1H), 5.53 (br. s., 1H), 4.97 (br. s., 1H), 4.81 (dt, *J*=11.9, 6.0 Hz, 1H), 4.59 (d, *J*=11.3 Hz, 1H), 4.48 (br. s., 1H), 3.99 - 3.87 (m, 1H), 3.78 - 3.64 (m, 1H), 2.77 - 2.68 (m,

1H), 2.60 (br. s., 1H), 2.40 - 2.24 (m, 2H), 1.91 - 1.28 (m, 19H), 1.13 (s, 3H), 0.97 - 0.83 (m, 8H), 0.74 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 802.7 (M^++1).

Preparation of Compound 5166 and Compound 5167



Compound 5166



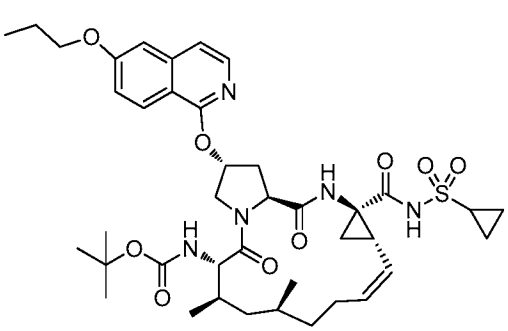
Compound 5167

Compounds 5166 and 5167 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

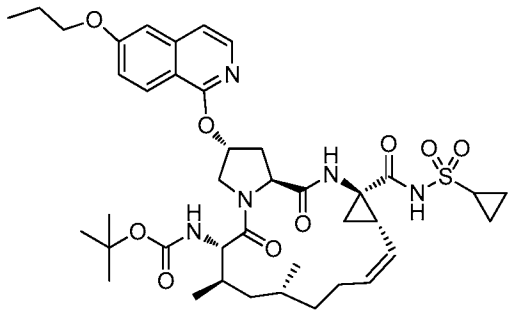
Compound 5166: 1,1,1,3,3,3-hexadeutero-2-(trideuteromethyl)propan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 805.8 (M^++1).

Compound 5167: 1,1,1,3,3,3-hexadeutero-2-(trideuteromethyl)propan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.10 (br. s., 1H), 8.03 (d, *J*=9.2 Hz, 1H), 7.93 (d, *J*=6.1 Hz, 1H), 7.37 - 7.23 (m, 2H), 7.17 (d, *J*=7.9 Hz, 1H), 7.07 (dd, *J*=9.0, 2.3 Hz, 1H), 5.82 (br. s., 1H), 5.53 (br. s., 1H), 4.97 (br. s., 1H), 4.81 (quin, *J*=6.0 Hz, 1H), 4.58 (d, *J*=10.7 Hz, 1H), 4.48 (br. s., 1H), 3.99 - 3.84 (m, 1H), 3.82 - 3.68 (m, 1H), 2.73 (d, *J*=18.0 Hz, 1H), 2.59 (br. s., 1H), 2.45 - 2.22 (m, 2H), 1.91 (d, *J*=12.8 Hz, 1H), 1.82 (d, *J*=6.7 Hz, 1H), 1.70 (br. s., 1H), 1.61 - 1.15 (m, 16H), 0.98 - 0.84 (m, 8H), 0.73 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 805.8 (M^++1).

Preparation of Compound 5168 and Compound 5169



Compound 5168



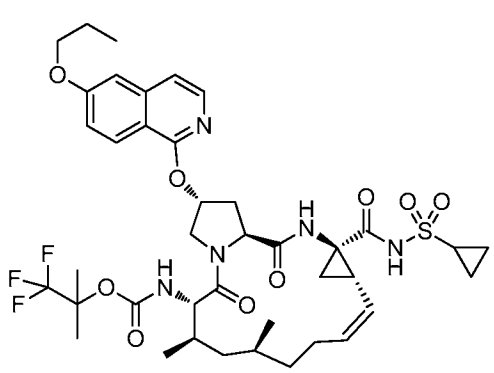
Compound 5169

Compounds 5168 and 5169 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

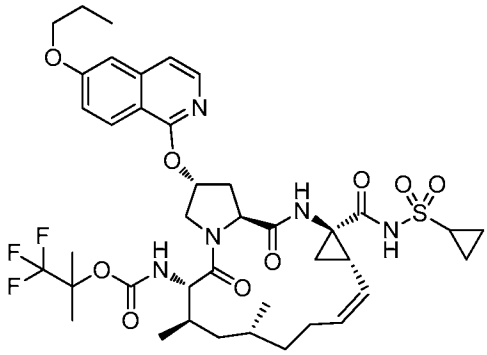
Compound 5168: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((6-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 782.4 (M^++1).

Compound 5169: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((6-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.18 (br. s., 1H), 9.10 (br. s., 1H), 8.04 (d, *J*=9.2 Hz, 1H), 7.97 - 7.92 (m, 1H), 7.36 - 7.25 (m, 2H), 7.16 (d, *J*=7.6 Hz, 1H), 7.10 (dd, *J*=9.0, 2.3 Hz, 1H), 5.80 (br. s., 1H), 5.47 (br. s., 1H), 5.09 (br. s., 1H), 4.55 (d, *J*=9.5 Hz, 1H), 4.41 (t, *J*=8.5 Hz, 1H), 4.08 (t, *J*=6.6 Hz, 2H), 3.93 - 3.83 (m, 1H), 3.79 - 3.63 (m, 1H), 2.85 (br. s., 1H), 2.56 (br. s., 1H), 2.37 - 2.21 (m, 2H), 1.94 - 1.17 (m, 19H), 1.11 - 0.83 (m, 14H), 0.70 (t, *J*=11.6 Hz, 1H); MS: MS *m/z* 782.4 (M^++1).

Preparation of Compound 5170 and Compound 5171



Compound 5170



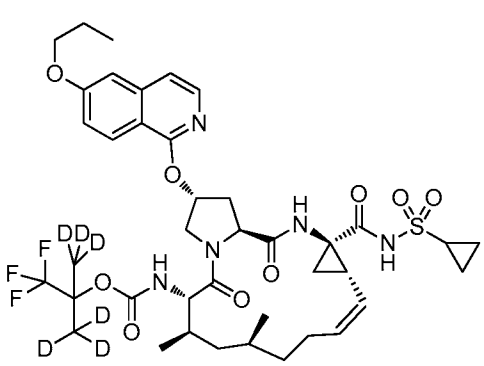
Compound 5171

Compounds 5170 and 5171 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

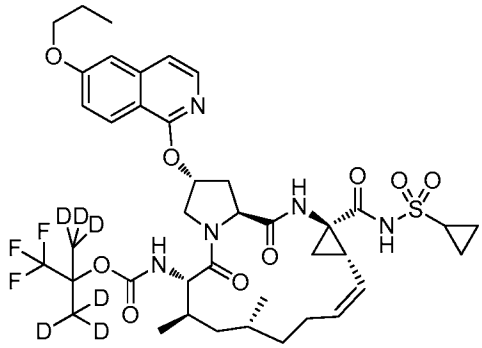
Compound 5170: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((6-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 836.3 (M^++1).

Compound 5171: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((6-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.20 (br. s., 1H), 9.00 (br. s., 1H), 8.06 - 7.92 (m, 2H), 7.82 (d, *J*=7.6 Hz, 1H), 7.36 - 7.26 (m, 2H), 7.15 (dd, *J*=9.2, 2.1 Hz, 1H), 5.81 (br. s., 1H), 5.51 (br. s., 1H), 5.07 (br. s., 1H), 4.60 - 4.42 (m, 2H), 4.08 (t, *J*=6.4 Hz, 2H), 3.97 - 3.86 (m, 1H), 3.70 (dd, *J*=10.7, 8.2 Hz, 1H), 2.90 (s, 1H), 2.65 (br. s., 1H), 2.61 (br. s., 1H), 2.36 - 2.22 (m, 2H), 1.95 - 1.74 (m, 4H), 1.72 (br. s., 1H), 1.59 (br. s., 1H), 1.52 (d, *J*=12.5 Hz, 1H), 1.41 (br. s., 1H), 1.37 (s, 4H), 1.21 - 1.07 (m, 5H), 1.02 (t, *J*=7.5 Hz, 5H), 0.97 - 0.85 (m, 7H), 0.73 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 836.3 (M^++1).

Preparation of Compound 5172 and Compound 5173



Compound 5172



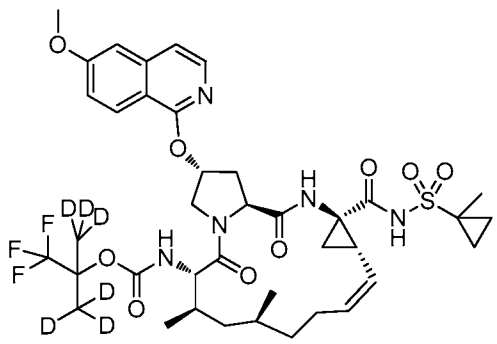
Compound 5173

Compounds 5172 and 5173 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

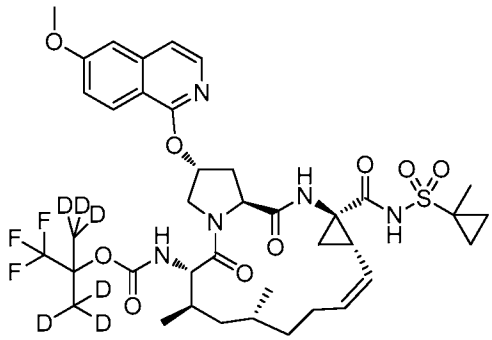
Compound 5172: 1,1,1,3,3,3-hexachloro-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((6-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 842.8 (M^++1).

Compound 5172: 1,1,1,3,3,3-hexachloro-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-((6-propoxyisoquinolin-1-yl)oxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.20 (br. s., 1H), 9.01 (br. s., 1H), 8.11 - 7.91 (m, 2H), 7.82 (d, *J*=7.6 Hz, 1H), 7.38 - 7.25 (m, 2H), 7.15 (dd, *J*=9.2, 2.4 Hz, 1H), 5.81 (br. s., 1H), 5.52 (br. s., 1H), 5.06 (br. s., 1H), 4.61 - 4.40 (m, 2H), 4.08 (t, *J*=6.6 Hz, 2H), 3.98 - 3.84 (m, 1H), 3.70 (dd, *J*=10.7, 8.2 Hz, 1H), 2.91 (s, 1H), 2.61 (br. s., 2H), 2.31 (ddd, *J*=13.7, 10.1, 4.0 Hz, 2H), 1.96 - 1.74 (m, 5H), 1.71 - 1.36 (m, 4H), 1.14 - 0.84 (m, 14H), 0.73 (t, *J*=12.7 Hz, 1H); MS: MS *m/z* 842.8 (M^++1).

Preparation of Compound 5174 and Compound 5175



Compound 5174



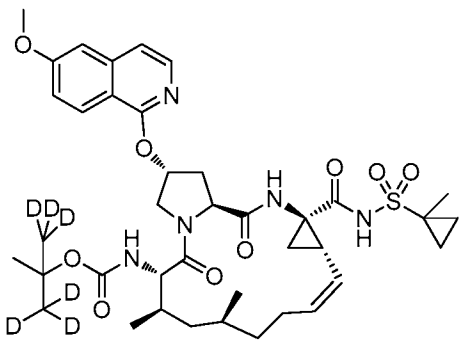
Compound 5175

Compounds 5174 and 5175 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

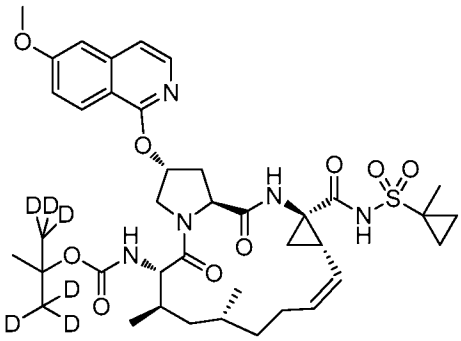
Compound 5174: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 828.6 (M^++1).

Compound 5175: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.04 (br. s., 1H), 9.14 (br. s., 1H), 8.09 - 7.92 (m, 2H), 7.83 (d, *J*=7.9 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.15 (dd, *J*=9.2, 2.4 Hz, 1H), 5.83 (br. s., 1H), 5.53 (br. s., 1H), 4.98 (br. s., 1H), 4.52 (br. s., 2H), 3.98 - 3.85 (m, 4H), 3.71 (dd, *J*=10.8, 8.1 Hz, 1H), 2.69 (br. s., 1H), 2.61 (br. s., 1H), 2.41 - 2.21 (m, 2H), 1.97 - 1.77 (m, 2H), 1.71 (br. s., 1H), 1.61 (br. s., 1H), 1.52 (br. s., 1H), 1.41 (br. s., 5H), 1.36 (br. s., 1H), 1.28 (br. s., 1H), 1.15 (br. s., 1H), 0.99 - 0.84 (m, 8H), 0.75 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 828.6 (M^++1).

Preparation of Compound 5176 and Compound 5177



Compound 5176



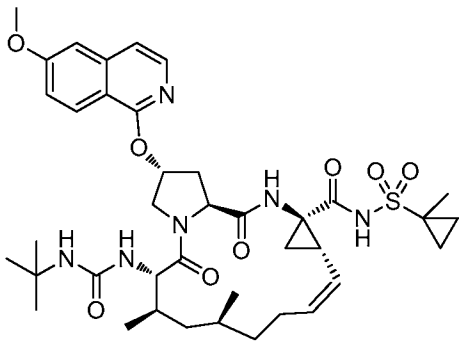
Compound 5177

Compounds 5176 and 5177 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

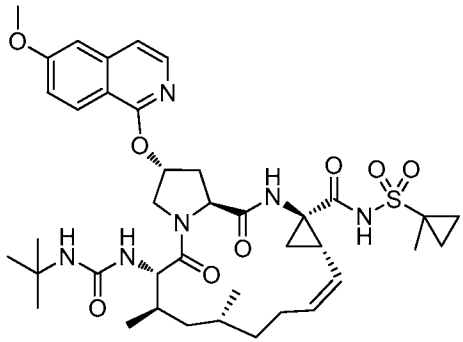
Compound 5176: 1,1,1,3,3,3-hexadeutero-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 774.6 (M^++1).

Compound 5177: 1,1,1,3,3,3-hexadeutero-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.10 (br. s., 1H), 8.05 (d, *J*=9.2 Hz, 1H), 7.96 (d, *J*=5.8 Hz, 1H), 7.39 - 7.26 (m, 2H), 7.18 (d, *J*=7.6 Hz, 1H), 7.11 (dd, *J*=9.2, 2.4 Hz, 1H), 5.82 (br. s., 1H), 5.52 (br. s., 1H), 4.97 (br. s., 1H), 4.59 (d, *J*=11.0 Hz, 1H), 4.47 (br. s., 1H), 3.98 - 3.83 (m, 4H), 3.73 (dd, *J*=10.4, 8.5 Hz, 1H), 2.78 - 2.66 (m, 1H), 2.60 (br. s., 1H), 2.41 - 2.22 (m, 2H), 1.96 - 1.78 (m, 2H), 1.70 - 1.26 (m, 10H), 1.15 (s, 4H), 0.95 - 0.83 (m, 8H), 0.74 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 774.7 (M^++1).

Preparation of Compound 5178 and Compound 5179



Compound 5178



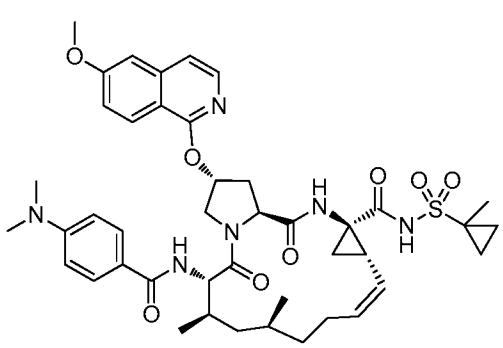
Compound 5179

Compounds 5178 and 5179 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

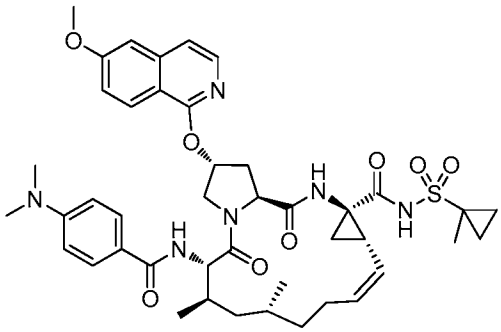
Compound 5178: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 767.4 (M^++1).

Compound 5179: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.05 (br. s., 1H), 9.06 (br. s., 1H), 8.06 (d, *J*=9.2 Hz, 1H), 7.96 (d, *J*=6.1 Hz, 1H), 7.38 - 7.23 (m, 2H), 7.09 (dd, *J*=9.2, 2.4 Hz, 1H), 5.96 (d, *J*=8.9 Hz, 1H), 5.83 (br. s., 1H), 5.58 (s, 1H), 5.52 (br. s., 1H), 4.98 (br. s., 1H), 4.56 (br. s., 1H), 4.42 (br. s., 1H), 3.98 - 3.78 (m, 5H), 2.75 (s, 1H), 2.57 (d, *J*=13.1 Hz, 1H), 2.41 - 2.20 (m, 2H), 1.96 - 1.81 (m, 1H), 1.78 - 1.63 (m, 2H), 1.59 (br. s., 1H), 1.40 (br. s., 7H), 1.28 (br. s., 1H), 1.22 - 1.10 (m, 1H), 1.06 (s, 9H), 0.92 (dd, *J*=13.0, 6.6 Hz, 8H), 0.80 - 0.70 (m, 1H); MS: MS *m/z* 767.4 (M^++1).

Preparation of Compound 5180 and Compound 5181



Compound 5180



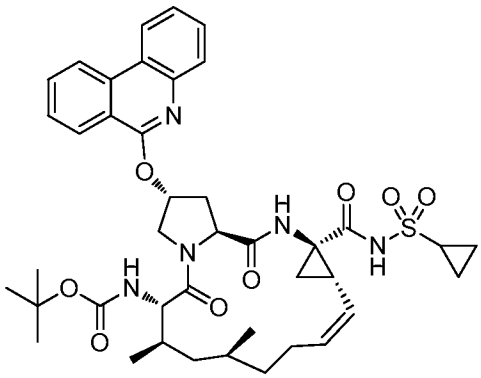
Compound 5181

Compounds 5180 and 5181 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

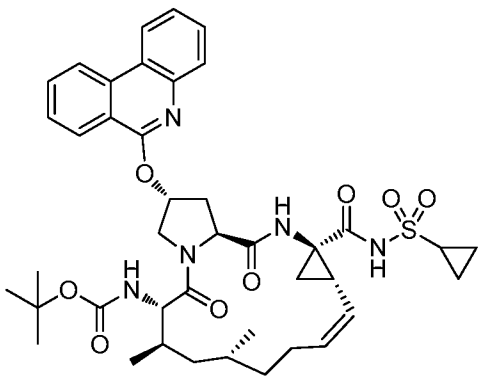
Compound 5180: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(4-(dimethylamino)benzamido)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 815.4 (M^++1).

Compound 5181: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(4-(dimethylamino)benzamido)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.06 (br. s., 1H), 9.03 (br. s., 1H), 8.28 (d, *J*=8.2 Hz, 1H), 8.08 - 7.86 (m, 2H), 7.64 - 7.55 (m, *J*=8.9 Hz, 2H), 7.39 - 7.25 (m, 2H), 7.04 (dd, *J*=8.9, 2.4 Hz, 1H), 6.66 - 6.54 (m, *J*=9.2 Hz, 2H), 5.85 (br. s., 1H), 5.55 (br. s., 1H), 5.09 - 4.91 (m, 1H), 4.80 (d, *J*=11.0 Hz, 1H), 4.56 - 4.34 (m, 1H), 4.23 (dd, *J*=10.5, 8.4 Hz, 1H), 3.98 (dd, *J*=11.3, 3.4 Hz, 1H), 3.92 (s, 4H), 2.97 (s, 6H), 2.82 - 2.70 (m, 1H), 2.70 - 2.60 (m, 1H), 2.42 - 2.23 (m, 2H), 2.20 - 2.04 (m, 1H), 2.04 - 1.94 (m, 1H), 1.81 - 1.20 (m, 10H), 0.96 (t, *J*=7.3 Hz, 6H), 0.90 (br. s., 2H), 0.82 (t, *J*=11.9 Hz, 1H); MS: MS *m/z* 815.4 (M^++1).

Preparation of Compound 5182 and Compound 5183



Compound 5182



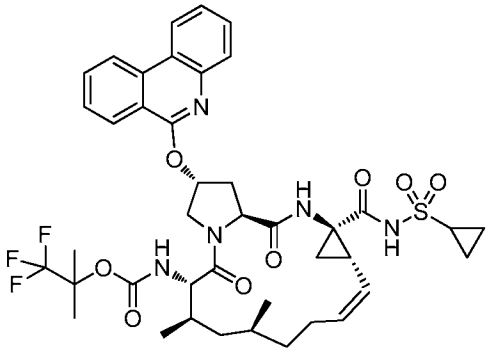
Compound 5183

Compounds 5182 and 5183 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

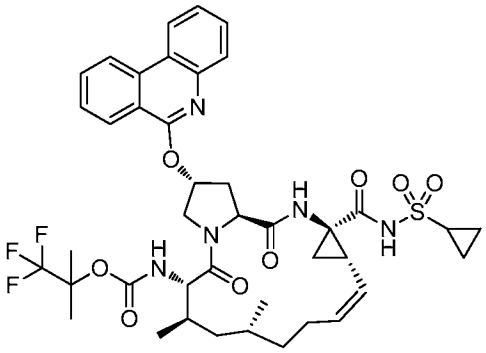
Compound 5182: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 774.3 (M^++1).

Compound 5183: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, METHANOL-d_4) δ ppm 8.63 (d, *J*=8.2 Hz, 1H), 8.53 (d, *J*=7.9 Hz, 1H), 8.33 (d, *J*=7.9 Hz, 1H), 7.93 - 7.80 (m, 2H), 7.73 - 7.57 (m, 2H), 7.57 - 7.47 (m, 1H), 6.09 (br. s., 1H), 5.55 (td, *J*=10.1, 6.0 Hz, 1H), 5.06 (t, *J*=9.6 Hz, 1H), 4.81 (d, *J*=11.6 Hz, 1H), 4.64 (dd, *J*=10.1, 7.0 Hz, 1H), 4.10 (dd, *J*=11.6, 3.7 Hz, 1H), 3.96 - 3.76 (m, 1H), 2.98 - 2.88 (m, 1H), 2.88 - 2.78 (m, 1H), 2.76 - 2.60 (m, 1H), 2.54 - 2.30 (m, 2H), 2.02 - 1.90 (m, 1H), 1.88 - 1.70 (m, 3H), 1.57 - 1.16 (m, 4H), 1.14 - 0.91 (m, 18H), 0.91 - 0.78 (m, 2H); MS: MS *m/z* 774.3 (M^++1).

Preparation of Compound 5184 and Compound 5185



Compound 5184



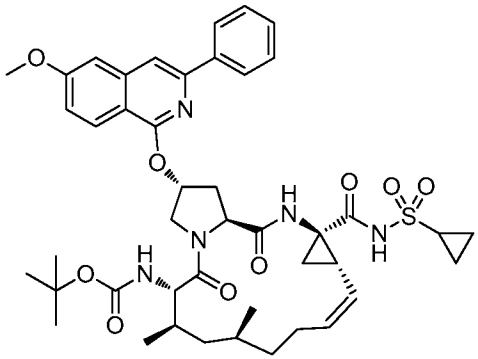
Compound 5185

Compounds 5184 and 5185 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

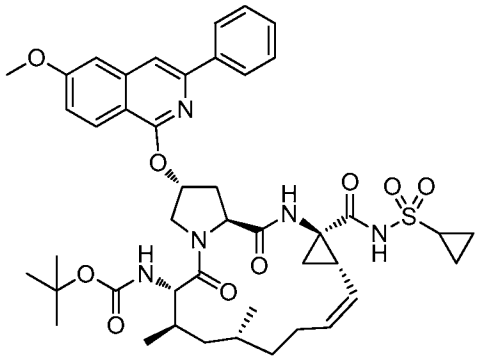
Compound 5184: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 828.4 (M^++1).

Compound 5185: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, METHANOL-d_4) δ ppm 8.65 (d, *J*=8.2 Hz, 1H), 8.55 (d, *J*=7.9 Hz, 1H), 8.32 (d, *J*=7.6 Hz, 1H), 7.94 - 7.83 (m, 2H), 7.72 - 7.60 (m, 2H), 7.57 - 7.48 (m, 1H), 6.06 (t, *J*=3.2 Hz, 1H), 5.56 (td, *J*=10.1, 5.6 Hz, 1H), 5.17 (t, *J*=9.8 Hz, 1H), 4.86 (d, *J*=12.2 Hz, 1H), 4.67 (dd, *J*=10.4, 7.0 Hz, 1H), 4.08 (dd, *J*=11.7, 3.2 Hz, 1H), 3.88 - 3.75 (m, 1H), 2.97 - 2.76 (m, 2H), 2.65 (q, *J*=9.2 Hz, 1H), 2.50 (ddd, *J*=14.0, 10.1, 4.3 Hz, 1H), 2.44 - 2.30 (m, 1H), 2.01 - 1.89 (m, 2H), 1.89 - 1.70 (m, 3H), 1.58 (dd, *J*=9.5, 5.2 Hz, 1H), 1.52 - 1.39 (m, 2H), 1.34 - 1.15 (m, 5H), 1.12 - 0.93 (m, 8H), 0.90 (s, 3H), 0.82 (t, *J*=11.7 Hz, 1H); MS: MS *m/z* 828.3 (M^++1).

Preparation of Compound 5186 and Compound 5187



Compound 5186



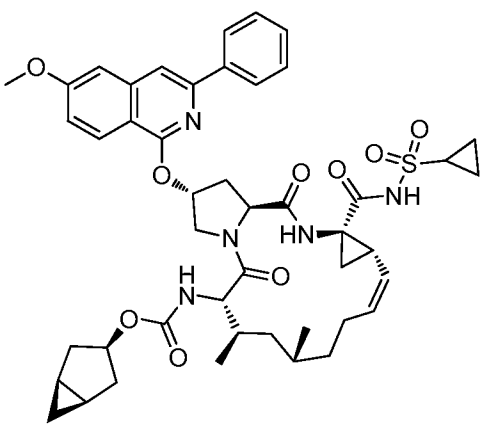
Compound 5187

Compounds 5186 and 5187 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

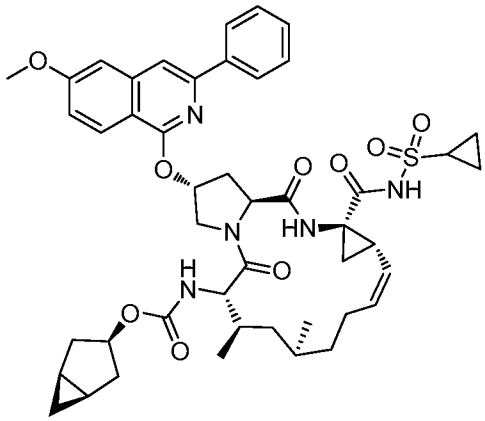
Compound 5186: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-phenylisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 830.4 (M^++1).

Compound 5187: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-phenylisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.22 (br. s., 1H), 8.94 (br. s., 1H), 8.26 - 8.17 (m, 2H), 8.07 (d, *J*=8.9 Hz, 1H), 8.00 - 7.92 (m, 1H), 7.58 - 7.50 (m, 2H), 7.47 - 7.35 (m, 2H), 7.21 (d, *J*=9.2 Hz, 1H), 7.10 (dd, *J*=8.9, 2.4 Hz, 1H), 5.98 (br. s., 1H), 5.52 (br. s., 1H), 5.07 (br. s., 1H), 4.62 (d, *J*=8.9 Hz, 1H), 4.46 (t, *J*=8.1 Hz, 1H), 4.02 - 3.88 (m, 4H), 3.76 (dd, *J*=10.7, 8.2 Hz, 1H), 2.91 (s, 1H), 2.79 - 2.66 (m, 2H), 2.41 - 2.22 (m, 2H), 1.92 (br. s., 1H), 1.84 (d, *J*=7.0 Hz, 1H), 1.73 (br. s., 1H), 1.59 (br. s., 1H), 1.55 (br. s., 1H), 1.43 (br. s., 1H), 1.40 - 1.33 (m, 1H), 1.21 (s, 9H), 1.10 (d, *J*=19.2 Hz, 2H), 0.95 - 0.85 (m, 9H), 0.75 (t, *J*=11.7 Hz, 1H); MS: MS *m/z* 830.4 (M^++1).

Preparation of Compound 5188 and Compound 5189



Compound 5188



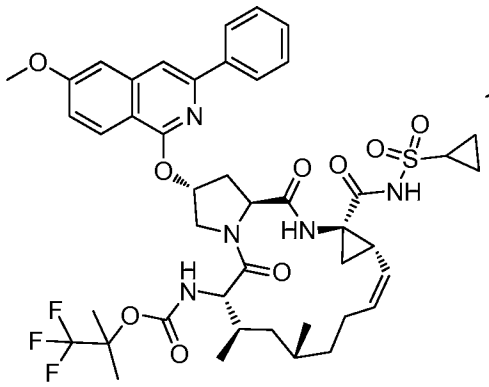
Compound 5189

Compounds 5188 and 5189 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

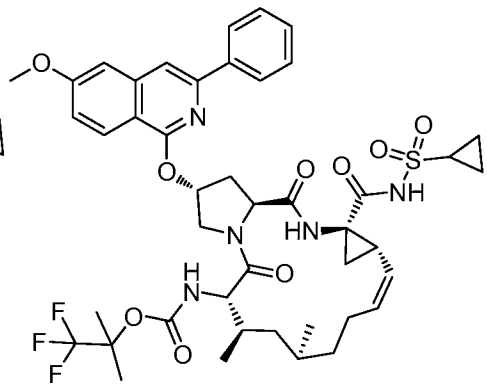
Compound 5188: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-phenylisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 854.4 (M^++1).

Compound 5189: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-phenylisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.18 (br. s., 1H), 8.90 (br. s., 1H), 8.20 (d, *J*=7.3 Hz, 2H), 8.05 (d, *J*=9.0 Hz, 1H), 8.00 - 7.92 (m, 1H), 7.59 - 7.50 (m, 2H), 7.48 - 7.35 (m, 3H), 7.16 (dd, *J*=9.0, 2.5 Hz, 1H), 6.00 (br. s., 1H), 5.52 (br. s., 1H), 5.07 (br. s., 1H), 4.72 (t, *J*=7.0 Hz, 1H), 4.62 - 4.37 (m, 2H), 4.01 (dd, *J*=11.2, 3.4 Hz, 1H), 3.94 (s, 3H), 3.84 - 3.74 (m, 1H), 2.91 (s, 1H), 2.76 - 2.65 (m, 2H), 2.44 - 2.21 (m, 2H), 2.04 - 1.90 (m, 2H), 1.90 - 1.80 (m, 2H), 1.69 (d, *J*=5.3 Hz, 1H), 1.65 - 1.50 (m, 3H), 1.50 - 1.33 (m, 3H), 1.29 - 1.05 (m, 5H), 0.95 (d, *J*=6.8 Hz, 5H), 0.88 (d, *J*=6.3 Hz, 3H), 0.76 (t, *J*=12.3 Hz, 1H), 0.44 - 0.31 (m, 2H); MS: MS *m/z* 854.4 (M^++1).

Preparation of Compound 5190 and Compound 5191



Compound 5190



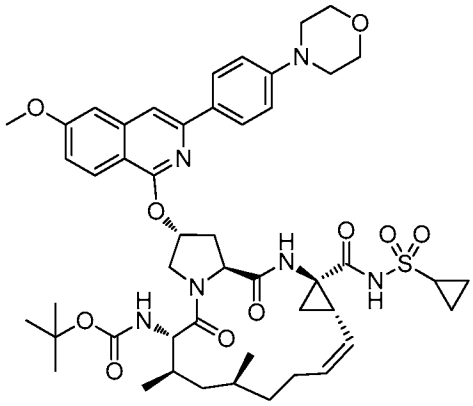
Compound 5191

Compounds 5190 and 5191 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

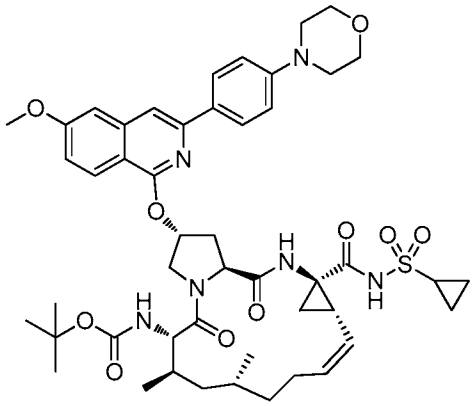
Compound 5190: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-phenylisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 884.3 (M^++1).

Compound 5191: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-phenylisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.21 (s, 1H), 8.98 (br. s., 1H), 8.24 - 8.16 (m, 2H), 8.03 (d, *J*=8.9 Hz, 1H), 7.98 - 7.94 (m, 1H), 7.86 (d, *J*=7.9 Hz, 1H), 7.58 - 7.52 (m, 2H), 7.47 - 7.38 (m, 2H), 7.14 (dd, *J*=9.2, 2.4 Hz, 1H), 6.00 (br. s., 1H), 5.62 - 5.44 (m, 1H), 5.07 (t, *J*=9.5 Hz, 1H), 4.63 - 4.44 (m, 2H), 4.03 - 3.88 (m, 4H), 3.74 (dd, *J*=10.7, 7.9 Hz, 1H), 2.97 - 2.90 (m, 1H), 2.78 - 2.64 (m, 2H), 2.45 - 2.25 (m, 2H), 1.89 (td, *J*=12.7, 6.4 Hz, 2H), 1.79 - 1.66 (m, 1H), 1.66 - 1.54 (m, 2H), 1.45 (d, *J*=13.4 Hz, 1H), 1.40 (s, 4H), 1.36 - 1.06 (m, 6H), 1.05 - 0.92 (m, 5H), 0.89 (d, *J*=6.4 Hz, 3H), 0.77 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 884.3 (M^++1).

Preparation of Compound 5192 and Compound 5193



Compound 5192



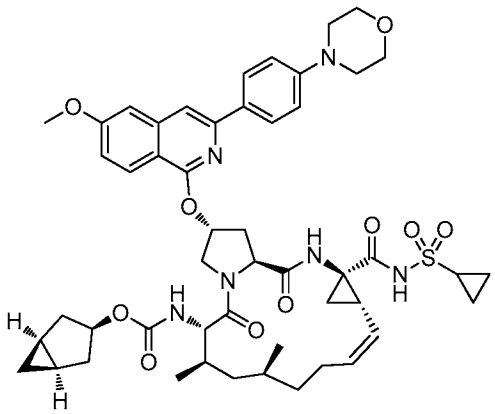
Compound 5193

Compounds 5192 and 5193 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

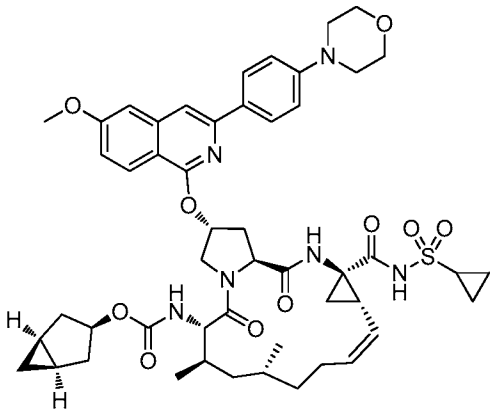
Compound 5192: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-(4-morpholinophenyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 915.7 (M^++1).

Compound 5193: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-(4-morpholinophenyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 915.7 (M^++1).

Preparation of Compound 5194 and Compound 5195



Compound 5194



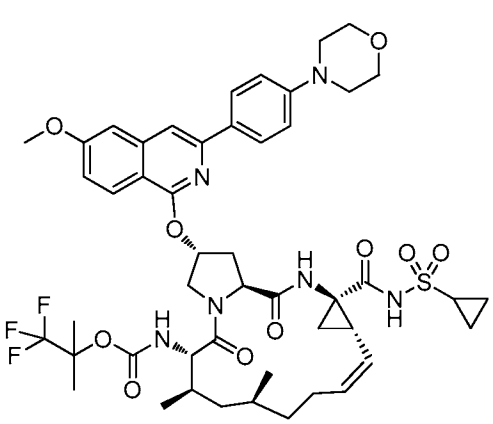
Compound 5195

Compounds 5194 and 5195 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

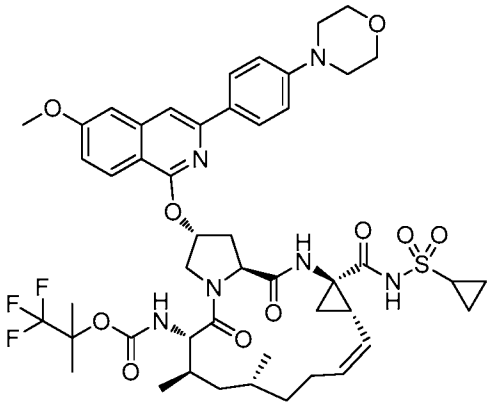
Compound 5194: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-(4-morpholinophenyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 939.7 (M^++1).

Compound 5195: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-(4-morpholinophenyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 939.7 (M^++1).

Preparation of Compound 5196 and Compound 5197



Compound 5196



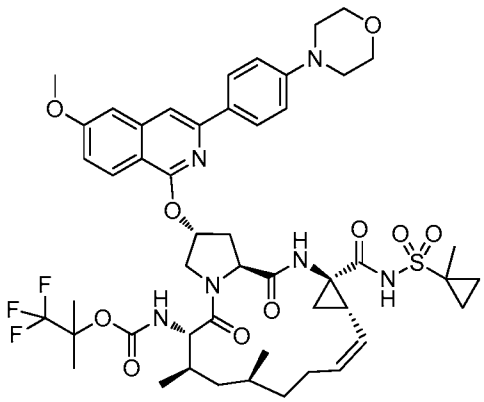
Compound 5197

Compounds 5196 and 5197 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

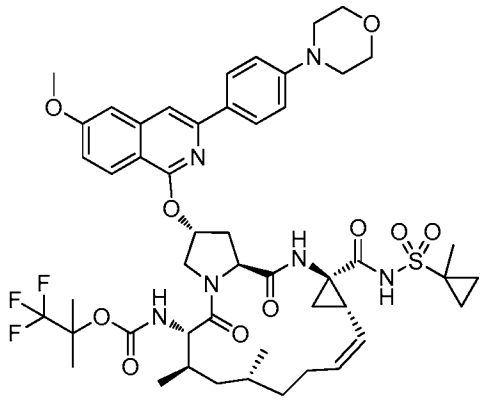
Compound 5196: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-(4-morpholinophenyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 969.4 (M^++1).

Compound 5197: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-3-(4-morpholinophenyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 969.4 (M^++1).

Preparation of Compound 5198 and Compound 5199



Compound 5198



Compound 5199

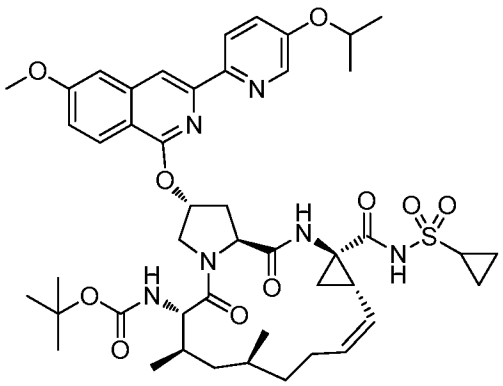
Compounds 5198 and 5199 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5198: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-methoxy-3-(4-morpholinophenyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 983.4 (M^++1).

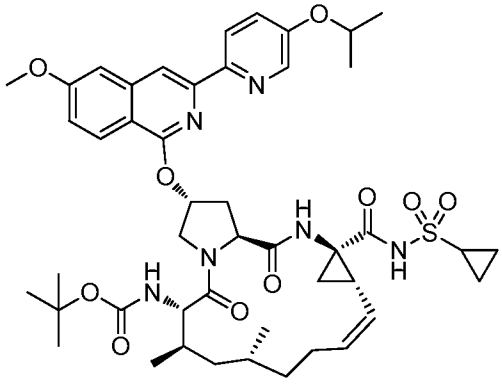
Compound 5199: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-methoxy-3-(4-morpholinophenyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.06 (s, 1H), 9.10 (s, 1H), 8.07 (d, *J*=8.9 Hz, 2H), 8.02 - 7.94 (m, 1H), 7.86 (d, *J*=7.9 Hz, 1H), 7.80 (s, 1H), 7.32 (d, *J*=2.4 Hz, 1H), 7.13 - 7.03 (m, 3H), 5.99 (br. s., 1H), 5.54 (d, *J*=6.1 Hz, 1H), 4.99 (t, *J*=9.6 Hz, 1H), 4.62 - 4.48 (m, 2H), 3.99 (dd, *J*=11.3, 3.1 Hz, 1H), 3.91 (s, 3H), 3.83 - 3.68 (m, 5H), 3.26 - 3.17 (m, 4H), 2.75 - 2.64 (m, 2H), 2.43 - 2.26 (m, 2H), 1.99 - 1.82 (m, 2H), 1.71 (d, *J*=6.1 Hz, 1H), 1.62 (br. s.,

1H), 1.53 (br. s., 1H), 1.50 - 1.33 (m, 9H), 1.33 - 1.16 (m, 5H), 0.97 - 0.86 (m, 8H), 0.78 (t, *J*=11.9 Hz, 1H); MS: MS *m/z* 983.4 (M^++1).

Preparation of Compound 5200 and Compound 5201



Compound 5200



Compound 5201

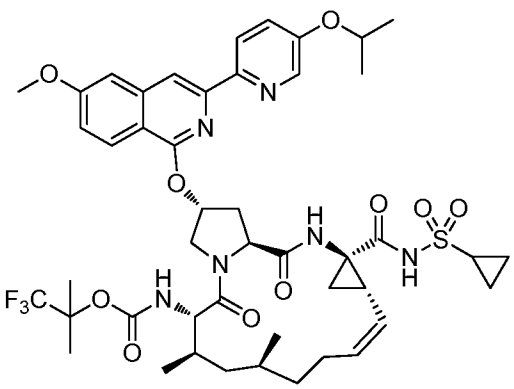
Compounds 5200 and 5201 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5200: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 889.8 (M^++1).

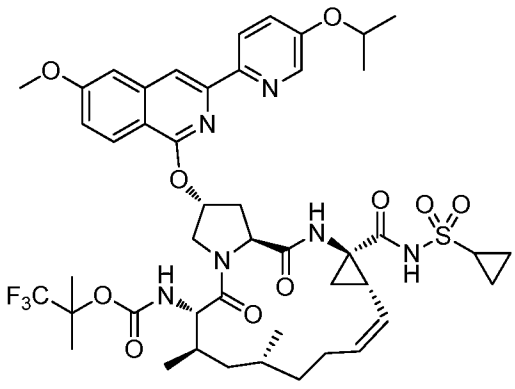
Compound 5201: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.23 (s, 1H), 8.95 (br. s., 1H), 8.42 - 8.34 (m, 2H), 8.26 (s, 1H), 8.06 (d, *J*=8.9 Hz, 1H), 7.58 (dd, *J*=8.9, 2.7 Hz, 1H), 7.45 (d, *J*=2.1 Hz, 1H), 7.22 (d, *J*=7.9 Hz, 1H), 7.09 (dd, *J*=9.0, 2.3 Hz, 1H), 5.98 (br. s., 1H), 5.59 - 5.48 (m, 1H), 5.07 (t, *J*=9.6 Hz, 1H), 4.81 (spt, *J*=6.0 Hz, 1H), 4.63 (d, *J*=11.6 Hz, 1H), 4.49 - 4.42 (m, 1H), 4.00 - 3.94 (m, 1H), 3.94 - 3.89 (m, 3H), 3.75 (dd, *J*=10.4, 8.5 Hz, 1H), 2.98 - 2.89 (m, 1H), 2.80 - 2.63 (m, 2H), 2.43 - 2.24 (m, 2H), 2.00 - 1.68 (m, 3H), 1.65 - 1.50 (m, 2H),

1.49 - 0.97 (m, 22H), 0.95 (d, *J*=6.7 Hz, 3H), 0.90 (d, *J*=6.4 Hz, 3H), 0.75 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 889.8 (M^++1).

Preparation of Compound 5202 and Compound 5203



Compound 5202



Compound 5203

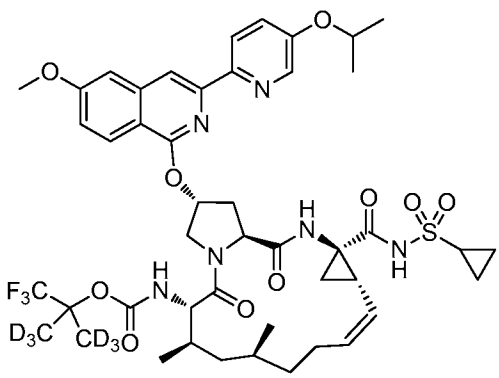
Compounds 5202 and 5203 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5202: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 943.6 (M^++1).

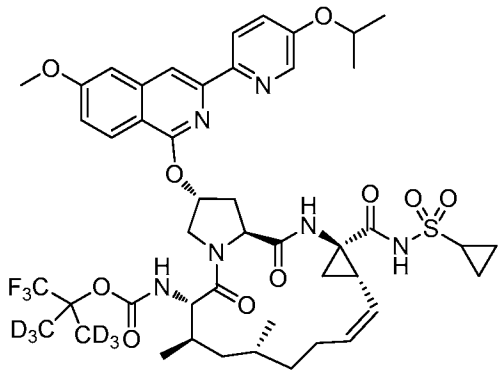
Compound 5203: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.23 (br. s., 1H), 8.99 (br. s., 1H), 8.41 - 8.35 (m, 2H), 8.27 (s, 1H), 8.03 (d, *J*=8.9 Hz, 1H), 7.86 (d, *J*=7.6 Hz, 1H), 7.58 (dd, *J*=8.7, 2.6 Hz, 1H), 7.47 (d, *J*=2.4 Hz, 1H), 7.13 (dd, *J*=9.2, 2.4 Hz, 1H), 6.00 (br. s., 1H), 5.60 - 5.48 (m, 1H), 5.12 - 5.01 (m, 1H), 4.81 (spt, *J*=6.0 Hz, 1H), 4.57 (d, *J*=10.7 Hz, 1H), 4.53 - 4.44 (m, 1H), 4.01 - 3.94 (m, 1H), 3.92 (s, 3H), 3.74 (dd, *J*=10.5, 8.1 Hz, 1H), 2.99 - 2.88 (m, 1H), 2.79 - 2.63 (m, 2H), 2.45 - 2.26 (m, 2H), 1.98 - 1.81 (m, 2H), 1.78 - 1.69 (m, 1H), 1.64 -

1.52 (m, 2H), 1.50 - 0.85 (m, 25H), 0.76 (t, *J*=11.7 Hz, 1H); MS: MS *m/z* 943.7 (M^++1).

Preparation of Compound 5204 and Compound 5205



Compound 5204



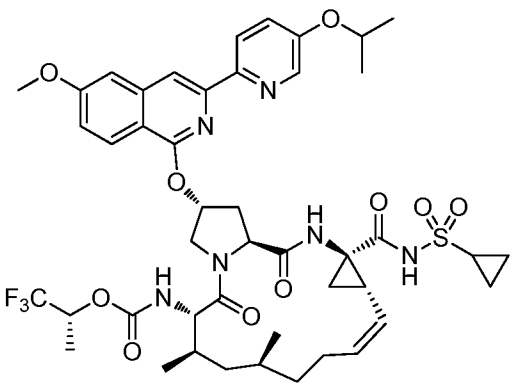
Compound 5205

Compounds 5204 and 5205 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

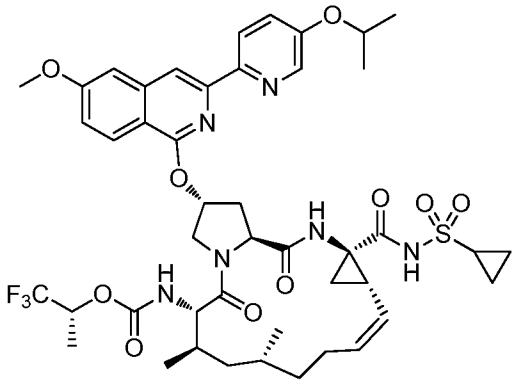
Compound 5204: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 949.8 (M^++1).

Compound 5205: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.23 (br. s., 1H), 8.99 (br. s., 1H), 8.41 - 8.34 (m, 2H), 8.27 (s, 1H), 8.03 (d, *J*=9.2 Hz, 1H), 7.85 (d, *J*=6.4 Hz, 1H), 7.58 (dd, *J*=8.5, 2.4 Hz, 1H), 7.46 (d, *J*=2.4 Hz, 1H), 7.13 (dd, *J*=9.2, 2.4 Hz, 1H), 6.00 (br. s., 1H), 5.60 - 5.46 (m, 1H), 5.13 - 5.01 (m, 1H), 4.81 (spt, *J*=6.1 Hz, 1H), 4.57 (d, *J*=9.8 Hz, 1H), 4.53 - 4.45 (m, 1H), 4.02 - 3.95 (m, 1H), 3.92 (s, 3H), 3.74 (dd, *J*=10.5, 8.1 Hz, 1H), 2.98 - 2.88 (m, 1H), 2.79 - 2.63 (m, 2H), 2.45 - 2.23 (m, 2H), 1.99 - 1.81 (m, 2H), 1.78 - 1.67 (m, 1H), 1.65 - 1.51 (m, 2H), 1.50 - 0.85 (m, 19H), 0.76 (t, *J*=11.6 Hz, 1H); MS: MS *m/z* 949.8 (M^++1).

Preparation of Compound 5206 and Compound 5207



Compound 5206



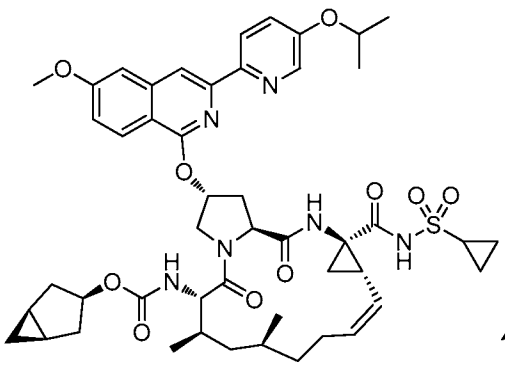
Compound 5207

Compounds 5206 and 5207 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

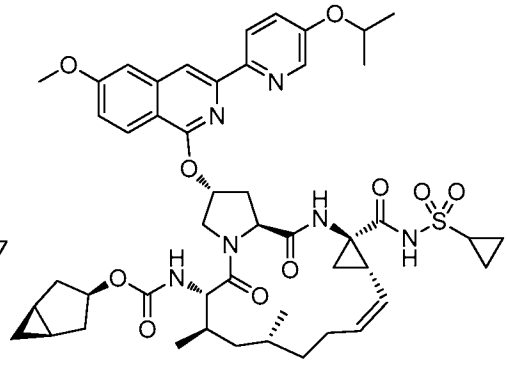
Compound 5206: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 929.7 (M^++1).

Compound 5207: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.22 (br. s., 1H), 8.95 (br. s., 1H), 8.42 - 8.34 (m, 2H), 8.27 (s, 1H), 8.11 (d, *J*=7.6 Hz, 1H), 8.00 (d, *J*=9.2 Hz, 1H), 7.58 (dd, *J*=8.7, 2.6 Hz, 1H), 7.46 (d, *J*=2.4 Hz, 1H), 7.07 (dd, *J*=9.0, 2.3 Hz, 1H), 5.99 (br. s., 1H), 5.58 - 5.49 (m, 1H), 5.15 - 5.03 (m, 1H), 4.89 - 4.75 (m, 2H), 4.57 (d, *J*=11.6 Hz, 1H), 4.52 - 4.42 (m, 1H), 4.03 - 3.97 (m, 1H), 3.91 (s, 3H), 3.81 (dd, *J*=10.8, 8.1 Hz, 1H), 2.97 - 2.87 (m, 1H), 2.79 - 2.62 (m, 2H), 2.45 - 2.24 (m, 2H), 1.99 - 1.83 (m, 2H), 1.77 - 1.67 (m, 1H), 1.58 (br. s., 2H), 1.50 - 0.86 (m, 22H), 0.78 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 929.7 (M^++1).

Preparation of Compound 5208 and Compound 5209



Compound 5208



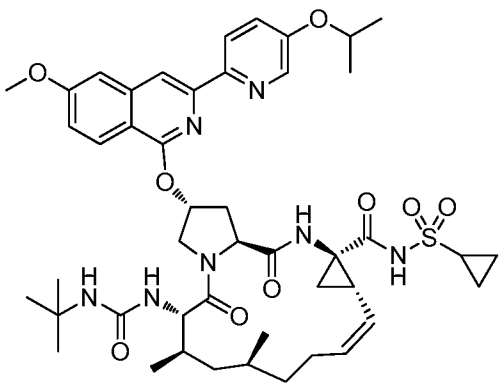
Compound 5209

Compounds 5208 and 5209 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

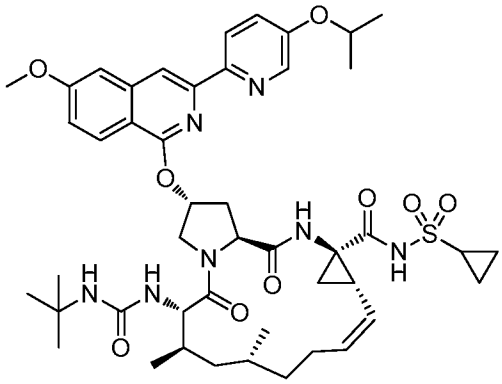
Compound 5208: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 913.7 (M^++1).

Compound 5209: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.23 (s, 1H), 8.92 (s, 1H), 8.40 - 8.35 (m, 2H), 8.27 (s, 1H), 8.04 (d, *J*=9.2 Hz, 1H), 7.57 (dd, *J*=8.7, 2.9 Hz, 1H), 7.47 (d, *J*=2.4 Hz, 1H), 7.44 (d, *J*=8.5 Hz, 1H), 7.15 (dd, *J*=9.0, 2.3 Hz, 1H), 6.00 (br. s., 1H), 5.59 - 5.50 (m, 1H), 5.08 (t, *J*=9.8 Hz, 1H), 4.80 (spt, *J*=6.0 Hz, 1H), 4.70 (t, *J*=6.7 Hz, 1H), 4.54 (d, *J*=11.0 Hz, 1H), 4.47 (dd, *J*=9.5, 7.3 Hz, 1H), 4.00 (dd, *J*=11.1, 3.2 Hz, 1H), 3.93 (s, 3H), 3.79 (dd, *J*=10.5, 9.0 Hz, 1H), 2.98 - 2.89 (m, 1H), 2.77 - 2.66 (m, 2H), 2.44 - 2.22 (m, 2H), 2.03 - 1.90 (m, 2H), 1.89 - 1.78 (m, 2H), 1.73 - 1.64 (m, 1H), 1.63 - 0.96 (m, 19H), 0.95 (d, *J*=6.7 Hz, 3H), 0.88 (d, *J*=6.4 Hz, 3H), 0.75 (t, *J*=12.4 Hz, 1H), 0.44 - 0.34 (m, 2H); MS: MS *m/z* 913.7 (M^++1).

Preparation of Compound 5210 and Compound 5211



Compound 5210



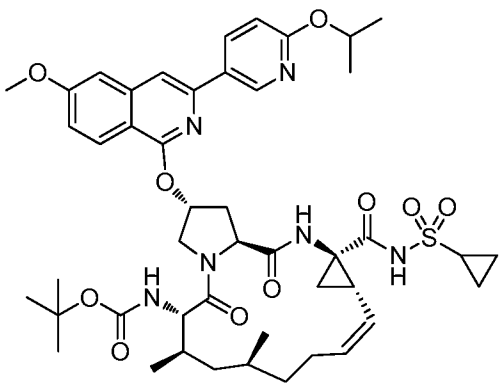
Compound 5211

Compounds 5210 and 5211 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

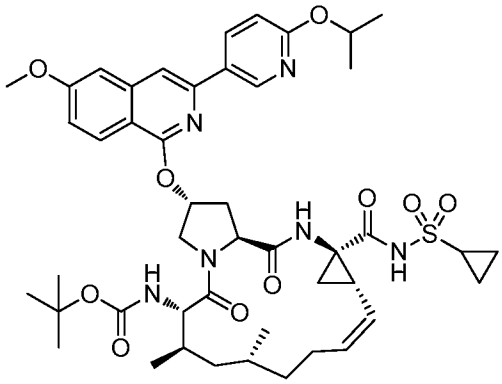
Compound 5210: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-N-(cyclopropylsulfonyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide; MS: MS *m/z* 888.8 (M^++1).

Compound 5211: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-N-(cyclopropylsulfonyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.24 (br. s., 1H), 8.92 (br. s., 1H), 8.39 (d, *J*=8.9 Hz, 1H), 8.36 (d, *J*=2.7 Hz, 1H), 8.26 (s, 1H), 8.08 (d, *J*=9.2 Hz, 1H), 7.58 (d, *J*=6.7 Hz, 1H), 7.45 (d, *J*=2.1 Hz, 1H), 7.07 (dd, *J*=9.0, 2.3 Hz, 1H), 5.98 (br. s., 2H), 5.62 (s, 1H), 5.57 - 5.49 (m, 1H), 5.12 - 5.04 (m, 1H), 4.80 (spt, *J*=6.1 Hz, 1H), 4.62 (d, *J*=11.9 Hz, 1H), 4.49 - 4.36 (m, 1H), 4.03 - 3.96 (m, 1H), 3.94 - 3.84 (m, 4H), 2.98 - 2.88 (m, 1H), 2.79 - 2.68 (m, 2H), 2.44 - 2.28 (m, 2H), 1.99 - 1.87 (m, 1H), 1.81 - 1.63 (m, 2H), 1.62 - 0.85 (m, 30H), 0.76 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 888.8 (M^++1).

Preparation of Compound 5212 and Compound 5213



Compound 5212



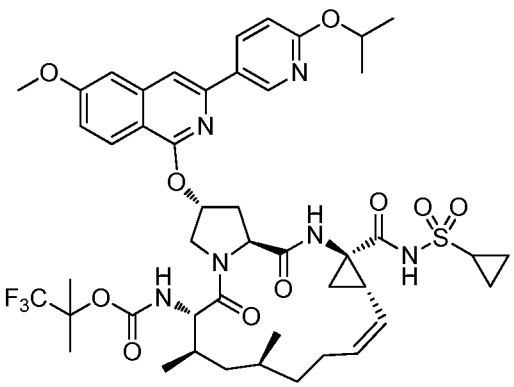
Compound 5213

Compounds 5212 and 5213 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

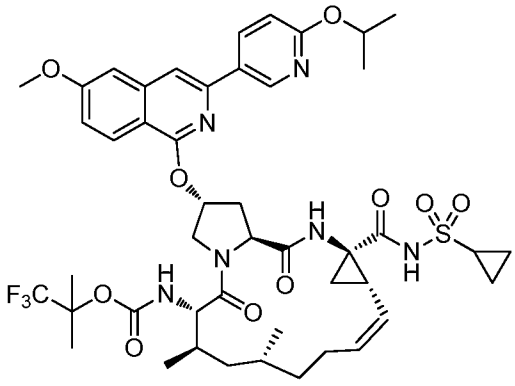
Compound 5212: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 889.7 (M^++1).

Compound 5213: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (br. s., 1H), 8.99 (d, *J*=2.4 Hz, 1H), 8.95 (br. s., 1H), 8.42 (dd, *J*=8.9, 2.4 Hz, 1H), 8.05 (d, *J*=9.2 Hz, 1H), 7.87 (s, 1H), 7.32 (d, *J*=2.1 Hz, 1H), 7.20 (d, *J*=7.3 Hz, 1H), 7.08 (dd, *J*=9.0, 2.3 Hz, 1H), 6.90 (d, *J*=8.5 Hz, 1H), 5.96 (br. s., 1H), 5.57 - 5.49 (m, 1H), 5.36 (spt, *J*=6.1 Hz, 1H), 5.13 - 5.00 (m, 1H), 4.62 (d, *J*=11.0 Hz, 1H), 4.46 (t, *J*=8.5 Hz, 1H), 3.96 (dd, *J*=10.8, 2.9 Hz, 1H), 3.92 (s, 3H), 3.75 (dd, *J*=10.4, 8.5 Hz, 1H), 2.91 (d, *J*=4.9 Hz, 1H), 2.78 - 2.65 (m, 2H), 2.42 - 2.24 (m, 2H), 2.00 - 1.68 (m, 3H), 1.66 - 1.51 (m, 2H), 1.49 - 0.96 (m, 22H), 0.95 (d, *J*=6.7 Hz, 3H), 0.89 (d, *J*=6.1 Hz, 3H), 0.75 (t, *J*=11.9 Hz, 1H); MS: MS *m/z* 889.7 (M^++1).

Preparation of Compound 5214 and Compound 5215



Compound 5214



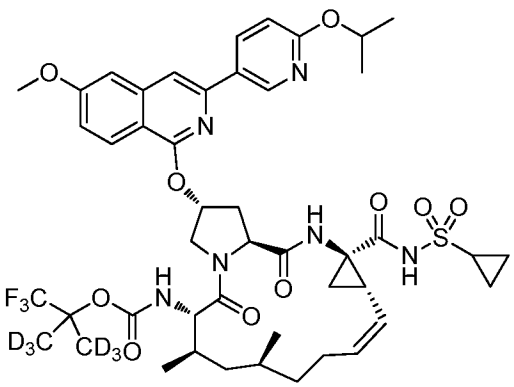
Compound 5215

Compounds 5214 and 5215 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

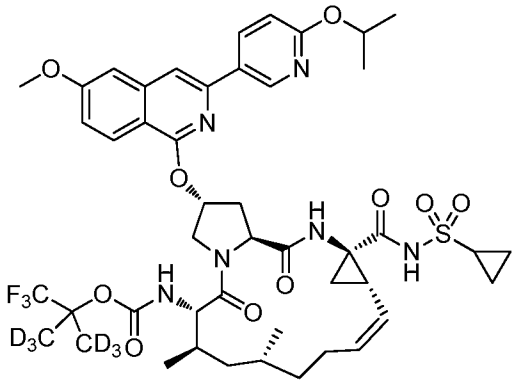
Compound 5214: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 943.7 (M^++1).

Compound 5215: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (br. s., 1H), 9.03 - 8.95 (m, 2H), 8.42 (dd, *J*=8.5, 2.4 Hz, 1H), 8.02 (d, *J*=9.2 Hz, 1H), 7.88 (s, 1H), 7.84 (d, *J*=7.6 Hz, 1H), 7.33 (d, *J*=2.4 Hz, 1H), 7.12 (dd, *J*=9.0, 2.3 Hz, 1H), 6.90 (d, *J*=8.9 Hz, 1H), 5.98 (br. s., 1H), 5.59 - 5.50 (m, 1H), 5.36 (spt, *J*=6.2 Hz, 1H), 5.15 - 5.02 (m, 1H), 4.57 (d, *J*=11.6 Hz, 1H), 4.54 - 4.47 (m, 1H), 3.97 (dd, *J*=11.4, 3.2 Hz, 1H), 3.93 (s, 3H), 3.74 (dd, *J*=10.7, 7.9 Hz, 1H), 2.98 - 2.88 (m, 1H), 2.78 - 2.63 (m, 2H), 2.42 - 2.24 (m, 2H), 2.00 - 1.81 (m, 2H), 1.78 - 1.67 (m, 1H), 1.65 - 1.52 (m, 2H), 1.50 - 0.97 (m, 19H), 0.95 (d, *J*=6.7 Hz, 3H), 0.89 (d, *J*=6.4 Hz, 3H), 0.77 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 943.6 (M^++1).

Preparation of Compound 5216 and Compound 5217



Compound 5216



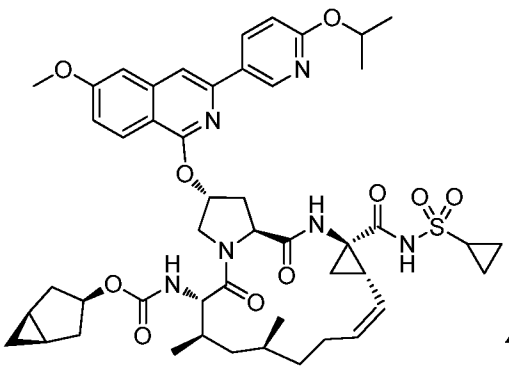
Compound 5217

Compounds 5216 and 5217 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

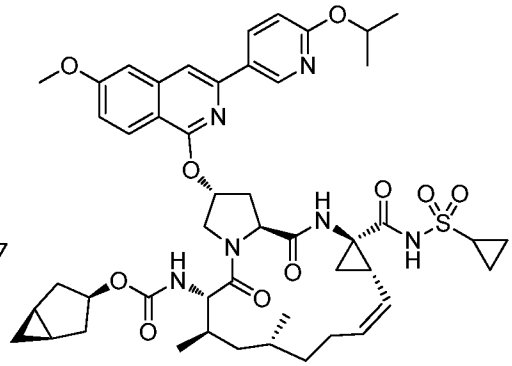
Compound 5216: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 949.7 (M^++1).

Compound 5217: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (s, 1H), 9.04 - 8.96 (m, 2H), 8.42 (dd, *J*=8.7, 2.6 Hz, 1H), 8.02 (d, *J*=9.2 Hz, 1H), 7.89 (s, 1H), 7.84 (d, *J*=7.9 Hz, 1H), 7.33 (d, *J*=2.1 Hz, 1H), 7.12 (dd, *J*=8.9, 2.4 Hz, 1H), 6.90 (d, *J*=8.5 Hz, 1H), 5.98 (br. s., 1H), 5.60 - 5.49 (m, 1H), 5.36 (spt, *J*=6.2 Hz, 1H), 5.15 - 5.01 (m, 1H), 4.57 (d, *J*=11.3 Hz, 1H), 4.54 - 4.45 (m, 1H), 3.97 (dd, *J*=11.3, 3.1 Hz, 1H), 3.93 (s, 3H), 3.74 (dd, *J*=10.7, 8.2 Hz, 1H), 2.91 (d, *J*=8.2 Hz, 1H), 2.70 (d, *J*=7.9 Hz, 2H), 2.45 - 2.24 (m, 2H), 1.99 - 1.81 (m, 2H), 1.78 - 1.68 (m, 1H), 1.65 - 1.52 (m, 2H), 1.50 - 0.97 (m, 13H), 0.95 (d, *J*=7.0 Hz, 3H), 0.89 (d, *J*=6.4 Hz, 3H), 0.77 (t, *J*=11.7 Hz, 1H); MS: MS *m/z* 949.7 (M^++1).

Preparation of Compound 5218 and Compound 5219



Compound 5218



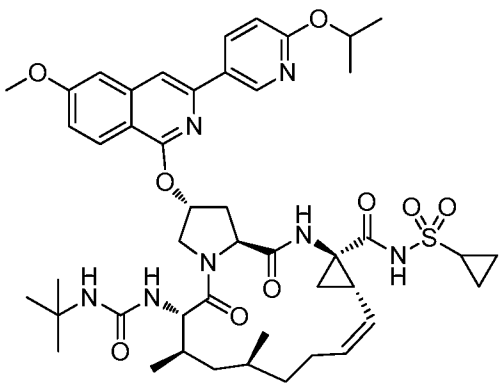
Compound 5219

Compounds 5218 and 5219 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

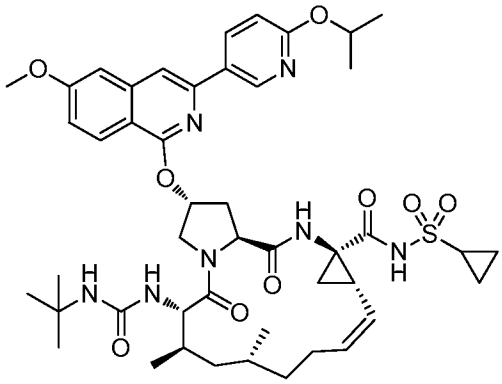
Compound 5218: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 913.7 (M^++1).

Compound 5219: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (br. s., 1H), 8.99 (d, *J*=2.4 Hz, 1H), 8.92 (br. s., 1H), 8.42 (dd, *J*=8.9, 2.4 Hz, 1H), 8.03 (d, *J*=9.2 Hz, 1H), 7.89 (s, 1H), 7.42 (d, *J*=8.2 Hz, 1H), 7.33 (d, *J*=2.4 Hz, 1H), 7.15 (dd, *J*=9.0, 2.3 Hz, 1H), 6.90 (d, *J*=8.9 Hz, 1H), 5.98 (br. s., 1H), 5.58 - 5.49 (m, 1H), 5.35 (spt, *J*=6.1 Hz, 1H), 5.07 (t, *J*=9.6 Hz, 1H), 4.69 (t, *J*=6.7 Hz, 1H), 4.52 (d, *J*=11.0 Hz, 1H), 4.49 - 4.43 (m, 1H), 3.99 (dd, *J*=11.1, 3.2 Hz, 1H), 3.93 (s, 3H), 3.81 - 3.76 (m, 1H), 2.98 - 2.89 (m, 1H), 2.80 - 2.63 (m, 2H), 2.43 - 2.24 (m, 2H), 2.02 - 1.91 (m, 2H), 1.88 - 1.76 (m, 2H), 1.72 - 1.64 (m, 1H), 1.63 - 0.97 (m, 19H), 0.95 (d, *J*=6.7 Hz, 3H), 0.87 (d, *J*=6.4 Hz, 3H), 0.76 (t, *J*=12.1 Hz, 1H), 0.42 - 0.31 (m, 2H); MS: MS *m/z* 913.7 (M^++1).

Preparation of Compound 5220 and Compound 5221



Compound 5220



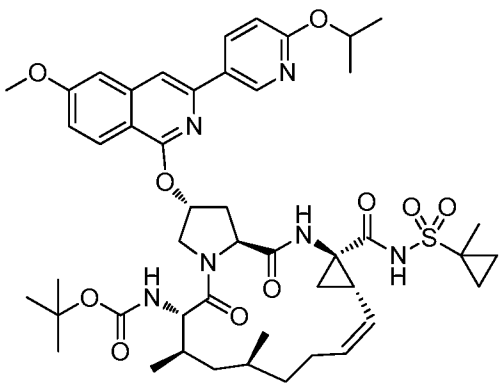
Compound 5221

Compounds 5220 and 5221 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

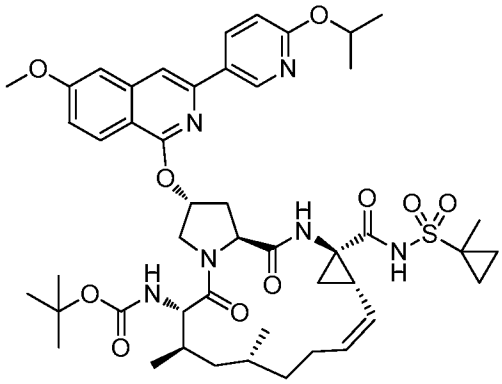
Compound 5220: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-N-(cyclopropylsulfonyl)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide; MS: MS *m/z* 888.7 (M^++1).

Compound 5221: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-N-(cyclopropylsulfonyl)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.99 (d, *J*=2.4 Hz, 1H), 8.92 (br. s., 1H), 8.42 (dd, *J*=8.7, 2.6 Hz, 1H), 8.06 (d, *J*=9.2 Hz, 1H), 7.87 (s, 1H), 7.31 (d, *J*=2.4 Hz, 1H), 7.07 (dd, *J*=9.2, 2.4 Hz, 1H), 6.89 (d, *J*=8.5 Hz, 1H), 6.02 - 5.94 (m, 2H), 5.60 (s, 1H), 5.57 - 5.47 (m, 1H), 5.36 (spt, *J*=6.2 Hz, 1H), 5.06 (t, *J*=10.2 Hz, 1H), 4.61 (d, *J*=10.1 Hz, 1H), 4.49 - 4.37 (m, 1H), 3.98 (dd, *J*=11.1, 3.2 Hz, 1H), 3.92 (s, 3H), 3.88 (t, *J*=9.8 Hz, 1H), 2.96 - 2.88 (m, 1H), 2.79 - 2.65 (m, 2H), 2.43 - 2.27 (m, 2H), 2.00 - 1.88 (m, 1H), 1.79 - 1.64 (m, 2H), 1.63 - 0.97 (m, 24H), 0.96 (d, *J*=6.7 Hz, 3H), 0.91 (d, *J*=6.4 Hz, 3H), 0.77 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 888.7 (M^++1).

Preparation of Compound 5222 and Compound 5223



Compound 5222



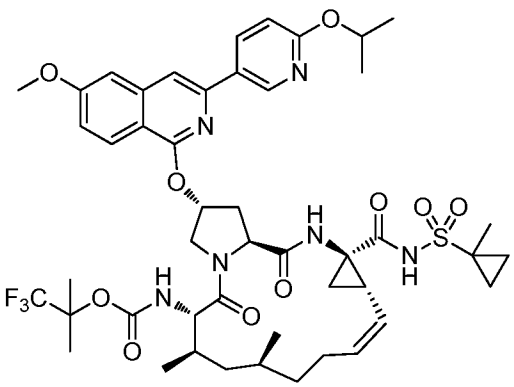
Compound 5223

Compounds 5222 and 5223 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

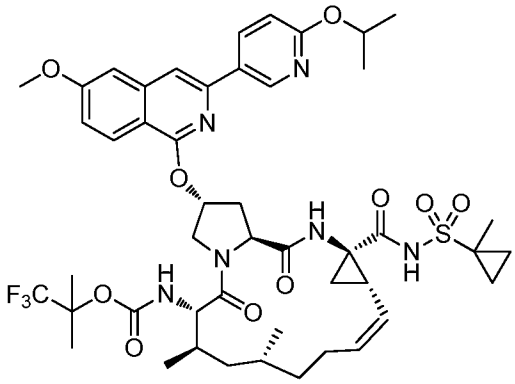
Compound 5222: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 903.7 (M^++1).

Compound 5223: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (br. s., 1H), 9.08 (br. s., 1H), 8.98 (d, *J*=2.1 Hz, 1H), 8.41 (dd, *J*=8.9, 2.4 Hz, 1H), 8.05 (d, *J*=8.9 Hz, 1H), 7.87 (s, 1H), 7.32 (d, *J*=2.1 Hz, 1H), 7.19 (d, *J*=8.2 Hz, 1H), 7.09 (dd, *J*=9.0, 2.3 Hz, 1H), 6.89 (d, *J*=8.9 Hz, 1H), 5.98 (br. s., 1H), 5.58 - 5.49 (m, 1H), 5.36 (spt, *J*=6.2 Hz, 1H), 5.04 - 4.93 (m, 1H), 4.63 (d, *J*=10.7 Hz, 1H), 4.55 - 4.46 (m, 1H), 3.99 (dd, *J*=11.2, 3.2 Hz, 1H), 3.92 (s, 3H), 3.75 (dd, *J*=10.2, 8.7 Hz, 1H), 2.78 - 2.64 (m, 2H), 2.42 - 2.27 (m, 2H), 1.98 - 1.79 (m, 2H), 1.75 - 1.67 (m, 1H), 1.65 - 1.58 (m, 1H), 1.56 - 1.10 (m, 24H), 0.99 - 0.85 (m, 8H), 0.76 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 903.7 (M^++1).

Preparation of Compound 5224 and Compound 5225



Compound 5224



Compound 5225

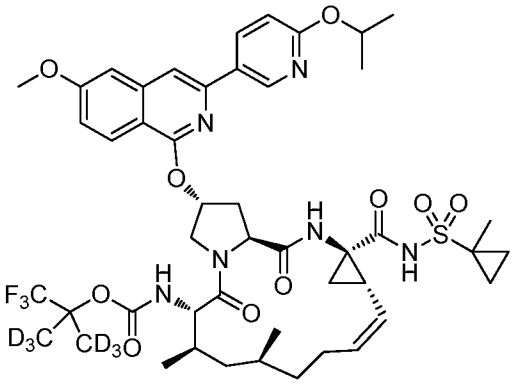
Compounds 5214 and 5215 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5224: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 957.6 (M^++1).

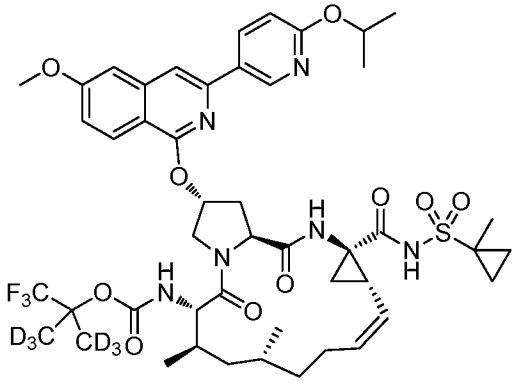
Compound 5225: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.12 (br. s., 1H), 8.99 (d, *J*=2.4 Hz, 1H), 8.41 (dd, *J*=8.9, 2.4 Hz, 1H), 8.02 (d, *J*=9.2 Hz, 1H), 7.88 (s, 1H), 7.83 (d, *J*=7.9 Hz, 1H), 7.33 (d, *J*=2.4 Hz, 1H), 7.13 (dd, *J*=9.0, 2.3 Hz, 1H), 6.90 (d, *J*=8.5 Hz, 1H), 6.00 (br. s., 1H), 5.57 - 5.50 (m, 1H), 5.36 (spt, *J*=6.1 Hz, 1H), 4.99 (t, *J*=9.8 Hz, 1H), 4.64 - 4.50 (m, 2H), 4.00 (dd, *J*=11.3, 3.1 Hz, 1H), 3.93 (s, 3H), 3.74 (dd, *J*=10.7, 8.2 Hz, 1H), 2.76 - 2.65 (m, 2H), 2.41 - 2.28 (m, 2H), 1.97 - 1.82 (m, 2H), 1.77 - 1.67 (m, 1H), 1.65 - 1.58 (m, 1H),

1.57 - 1.50 (m, 1H), 1.50 - 1.08 (m, 20H), 0.98 - 0.85 (m, 8H), 0.79 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 957.7 (M^++1).

Preparation of Compound 5226 and Compound 5227



Compound 5226



Compound 5227

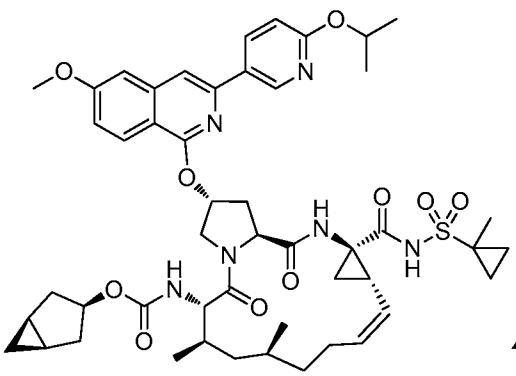
Compounds 5226 and 5227 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5226: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 963.7 (M^++1).

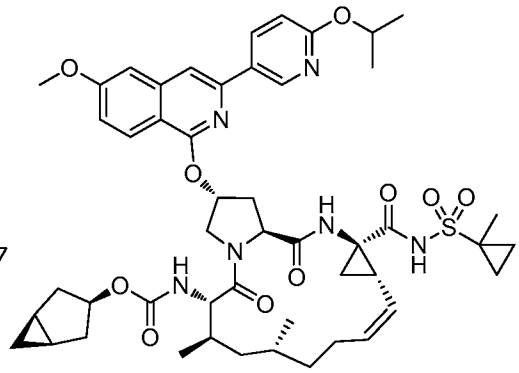
Compound 5227: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.12 (br. s., 1H), 8.99 (d, *J*=2.4 Hz, 1H), 8.41 (dd, *J*=8.5, 2.4 Hz, 1H), 8.02 (d, *J*=9.2 Hz, 1H), 7.88 (s, 1H), 7.84 (d, *J*=7.9 Hz, 1H), 7.33 (d, *J*=2.1 Hz, 1H), 7.13 (dd, *J*=9.2, 2.4 Hz, 1H), 6.90 (d, *J*=8.5 Hz, 1H), 5.99 (br. s., 1H), 5.60 - 5.48 (m, 1H), 5.36 (spt, *J*=6.1 Hz, 1H), 4.99 (t, *J*=9.8 Hz, 1H), 4.65 - 4.47 (m, 2H), 3.99 (dd,

J=11.3, 3.4 Hz, 1H), 3.93 (s, 3H), 3.74 (dd, *J*=10.8, 8.1 Hz, 1H), 2.77 - 2.66 (m, 2H), 2.42 - 2.30 (m, 2H), 1.97 - 1.80 (m, 2H), 1.76 - 1.67 (m, 1H), 1.66 - 1.59 (m, 1H), 1.57 - 1.50 (m, 1H), 1.50 - 1.10 (m, 14H), 1.00 - 0.85 (m, 8H), 0.78 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 963.7 (M^++1).

Preparation of Compound 5218 and Compound 5219



Compound 5228



Compound 5229

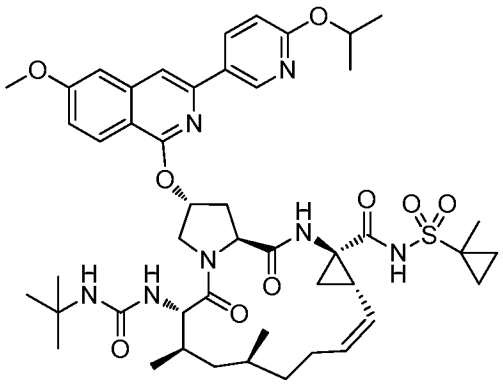
Compounds 5228 and 5229 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5228: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 927.7 (M^++1).

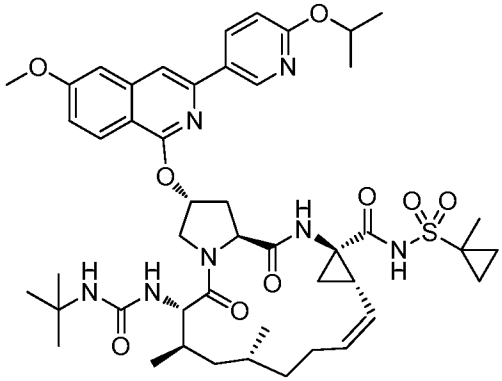
Compound 5229: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (br. s., 1H), 9.05 (br. s., 1H), 8.98 (d, *J*=2.4 Hz, 1H), 8.41 (dd, *J*=8.5, 2.4 Hz, 1H), 8.02 (d, *J*=9.2 Hz, 1H), 7.89 (s, 1H), 7.42 (d, *J*=8.2 Hz, 1H), 7.33 (d, *J*=2.1 Hz, 1H), 7.15 (dd, *J*=9.2, 2.4 Hz, 1H), 6.90 (d, *J*=8.5 Hz, 1H), 6.00 (br. s., 1H), 5.58 -

5.48 (m, 1H), 5.36 (spt, *J*=6.2 Hz, 1H), 5.09 - 4.93 (m, 1H), 4.66 (t, *J*=6.7 Hz, 1H), 4.58 - 4.45 (m, 2H), 4.01 (dd, *J*=11.3, 3.1 Hz, 1H), 3.93 (s, 3H), 3.78 (t, *J*=9.8 Hz, 1H), 2.79 - 2.62 (m, 2H), 2.42 - 2.24 (m, 2H), 2.01 - 1.73 (m, 4H), 1.72 - 1.08 (m, 21H), 1.00 - 0.83 (m, 8H), 0.77 (t, *J*=12.4 Hz, 1H), 0.41 - 0.31 (m, 2H); MS: MS *m/z* 927.7 (M^++1).

Preparation of Compound 5230 and Compound 5231



Compound 5230



Compound 5231

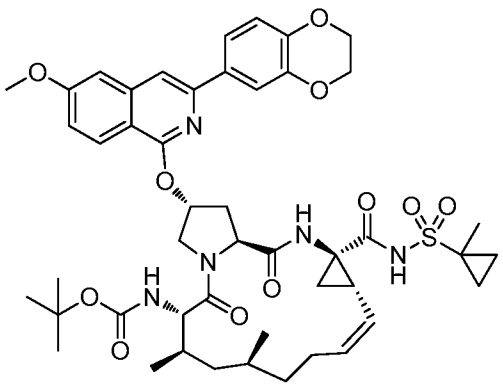
Compounds 5230 and 5231 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5230: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide; MS: MS *m/z* 902.7 (M^++1).

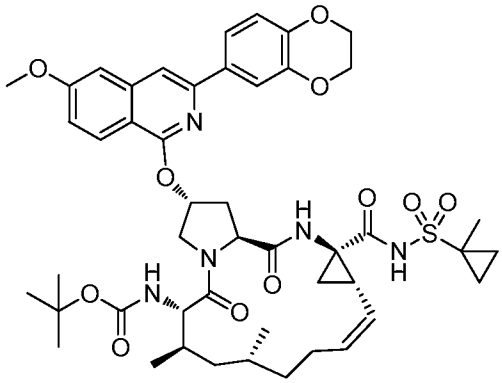
Compound 5231: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-2-((3-(6-isopropoxypyridin-3-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.07 (br. s., 1H), 9.05 (br. s., 1H), 8.98 (d, *J*=2.1 Hz, 1H), 8.41 (dd, *J*=8.9, 2.4 Hz, 1H), 8.06 (d, *J*=8.9 Hz, 1H), 7.87 (s, 1H), 7.32 (d, *J*=2.4 Hz, 1H), 7.07 (dd, *J*=8.9, 2.4 Hz, 1H), 6.89 (d, *J*=8.5 Hz, 1H), 5.98 (br. s., 2H), 5.59 (s, 1H), 5.57 - 5.46 (m, 1H), 5.36 (spt, *J*=6.2 Hz, 1H), 5.07 -

4.91 (m, 1H), 4.70 - 4.55 (m, 1H), 4.51 - 4.37 (m, 1H), 4.00 (dd, *J*=11.1, 3.5 Hz, 1H), 3.94 - 3.84 (m, 4H), 2.81 - 2.63 (m, 2H), 2.42 - 2.27 (m, 2H), 1.92 (s, 1H), 1.79 - 0.83 (m, 35H), 0.81 - 0.73 (m, 1H); MS: MS *m/z* 902.7 (M^++1).

Preparation of Compound 5232 and Compound 5233



Compound 5232



Compound 5233

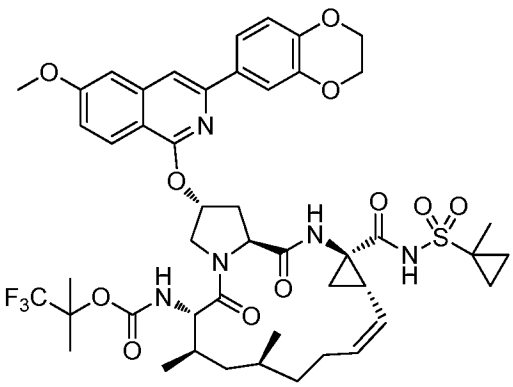
Compounds 5232 and 5233 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5232: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 902.1 (M^++1).

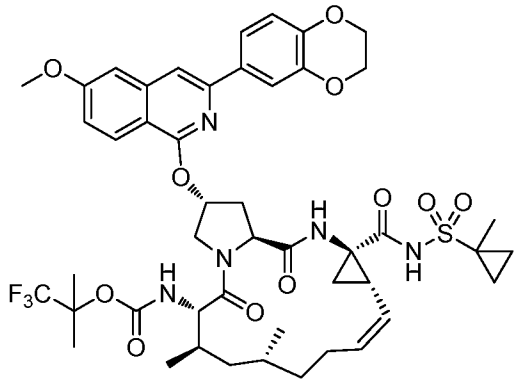
Compound 5233: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.07 (br. s., 1H), 9.06 (br. s., 1H), 8.03 (d, *J*=9.2 Hz, 1H), 7.82 (s, 1H), 7.69 (s, 1H), 7.66 (dd, *J*=8.5, 1.8 Hz, 1H), 7.33 (d, *J*=2.1 Hz, 1H), 7.22 (d, *J*=7.9 Hz, 1H), 7.05 (dd, *J*=9.0, 2.3 Hz, 1H), 6.99 (d, *J*=8.5 Hz, 1H), 5.96 (br. s., 1H), 5.58 - 5.50 (m, 1H), 5.03 - 4.95 (m, 1H), 4.61 (d, *J*=11.9 Hz, 1H), 4.52 - 4.44 (m, 1H), 4.32 (s, 4H), 3.97 (dd, *J*=11.1, 2.9 Hz, 1H), 3.91 (s, 3H), 3.78 - 3.72 (m, 1H), 2.78 - 2.63 (m, 2H), 2.42 -

2.29 (m, 2H), 1.97 - 1.78 (m, 2H), 1.76 - 1.67 (m, 1H), 1.64 - 1.58 (m, 1H), 1.56 - 1.08 (m, 18H), 1.01 - 0.85 (m, 8H), 0.76 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 902.1 (M^++1).

Preparation of Compound 5234 and Compound 5235



Compound 5234



Compound 5235

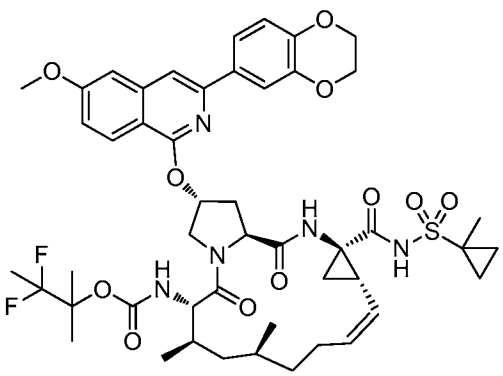
Compounds 5234 and 5235 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5234: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 956.5 (M^++1).

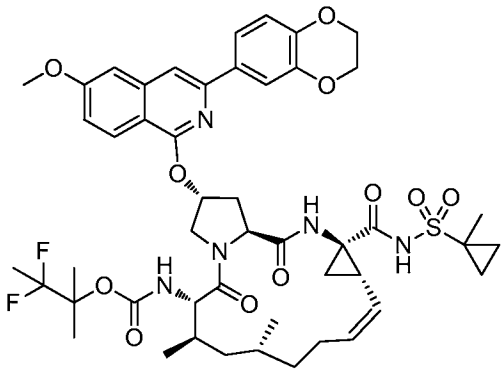
Compound 5235: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.10 (s, 1H), 7.99 (d, *J*=9.2 Hz, 1H), 7.86 (d, *J*=7.9 Hz, 1H), 7.83 (s, 1H), 7.72 - 7.65 (m, 2H), 7.34 (d, *J*=2.4 Hz, 1H), 7.09 (dd, *J*=9.0, 2.3 Hz, 1H), 7.00 (d, *J*=8.2 Hz, 1H), 5.98 (br. s., 1H), 5.60 - 5.47 (m, 1H), 5.00 (t, *J*=9.8 Hz, 1H), 4.60 -

4.49 (m, 2H), 4.32 (s, 4H), 3.97 (dd, *J*=11.3, 3.4 Hz, 1H), 3.92 (s, 3H), 3.73 (dd, *J*=10.7, 8.2 Hz, 1H), 2.77 - 2.65 (m, 2H), 2.41 - 2.31 (m, 2H), 1.97 - 1.81 (m, 2H), 1.76 - 1.67 (m, 1H), 1.65 - 1.58 (m, 1H), 1.56 - 1.50 (m, 1H), 1.50 - 1.10 (m, 14H), 0.98 - 0.86 (m, 8H), 0.78 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 956.5 (M^++1).

Preparation of Compound 5236 and Compound 5237



Compound 5236



Compound 5237

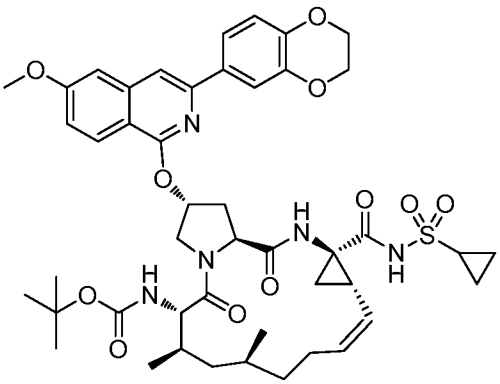
Compounds 5236 and 5237 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5236: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 952.5 (M^++1).

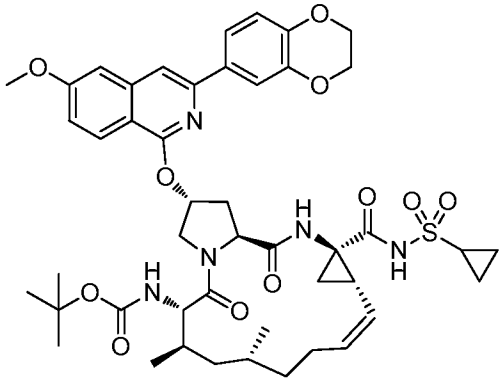
Compound 5237: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (br. s., 1H), 9.07 (br. s., 1H), 8.00 (d, *J*=9.2 Hz, 1H), 7.83 (s, 1H), 7.73 - 7.61 (m, 3H), 7.34 (d, *J*=2.1 Hz, 1H), 7.08 (dd, *J*=9.2, 2.4 Hz, 1H), 7.00 (d, *J*=8.5 Hz, 1H),

5.98 (br. s., 1H), 5.59 - 5.49 (m, 1H), 5.06 - 4.95 (m, 1H), 4.61 - 4.46 (m, 2H), 4.32 (s, 4H), 3.98 (dd, *J*=11.0, 3.1 Hz, 1H), 3.91 (s, 3H), 3.75 (dd, *J*=10.4, 8.5 Hz, 1H), 2.80 - 2.67 (m, 2H), 2.42 - 2.29 (m, 2H), 1.99 - 1.80 (m, 2H), 1.77 - 1.67 (m, 1H), 1.66 - 1.05 (m, 19H), 1.00 - 0.84 (m, 8H), 0.78 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 952.5 (M^++1).

Preparation of Compound 5238 and Compound 5239



Compound 5238



Compound 5239

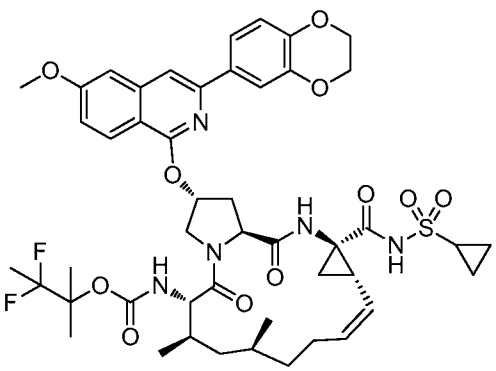
Compounds 5238 and 5239 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5238: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 888.5 (M^++1).

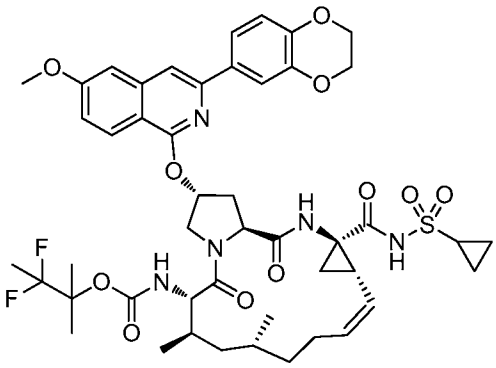
Compound 5239: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.92 (br. s., 1H), 8.03 (d, *J*=9.2 Hz, 1H), 7.82 (s, 1H), 7.70 (d, *J*=1.5 Hz, 1H), 7.67 (dd, *J*=8.4, 2.0 Hz, 1H), 7.33 (d, *J*=2.1 Hz, 1H), 7.21 (d, *J*=7.9 Hz, 1H), 7.05 (dd, *J*=9.2, 2.1 Hz, 1H), 7.00 (d, *J*=8.2 Hz, 1H), 5.94 (br. s., 1H), 5.58 - 5.47 (m, 1H), 5.07 (t, *J*=9.6 Hz, 1H), 4.61 (d, *J*=11.6 Hz, 1H), 4.49 - 4.39 (m, 1H), 4.32 (s,

4H), 3.95 (dd, *J*=11.6, 3.1 Hz, 1H), 3.91 (s, 3H), 3.75 (dd, *J*=10.4, 8.5 Hz, 1H), 2.98 - 2.88 (m, 1H), 2.79 - 2.66 (m, 2H), 2.40 - 2.23 (m, 2H), 2.01 - 1.68 (m, 3H), 1.65 - 1.51 (m, 2H), 1.49 - 1.32 (m, 2H), 1.30 - 0.96 (m, 14H), 0.95 (d, *J*=7.0 Hz, 3H), 0.90 (d, *J*=6.4 Hz, 3H), 0.75 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 888.5 (M^++1).

Preparation of Compound 5240 and Compound 5241



Compound 5240



Compound 5241

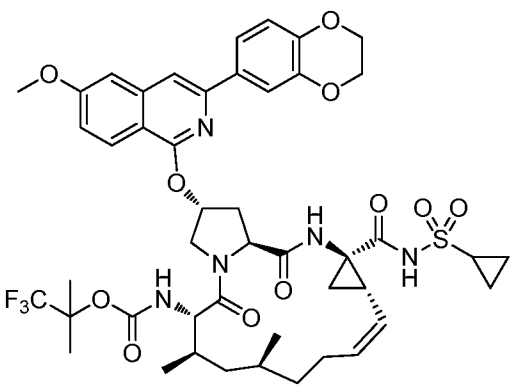
Compounds 5240 and 5241 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5240: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 938.5 (M^++1).

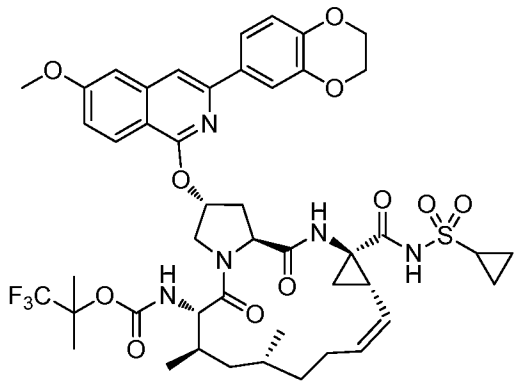
Compound 5241: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.22 (br. s., 1H), 8.93 (br. s., 1H), 8.00 (d, *J*=8.9 Hz, 1H), 7.83 (s, 1H), 7.70 (d, *J*=1.5 Hz, 1H), 7.67 (dd, *J*=8.4, 2.0 Hz, 1H), 7.64 (d, *J*=6.4 Hz, 1H), 7.33 (d, *J*=2.1 Hz, 1H), 7.07 (dd, *J*=9.0, 2.3 Hz, 1H), 7.00 (d, *J*=8.2 Hz, 1H), 5.95 (br. s., 1H), 5.59 - 5.47 (m, 1H), 5.17 - 5.02 (m, 1H), 4.58 - 4.50 (m,

1H), 4.50 - 4.42 (m, 1H), 4.32 (s, 4H), 3.96 (dd, *J*=11.1, 2.9 Hz, 1H), 3.91 (s, 3H), 3.75 (dd, *J*=10.5, 8.4 Hz, 1H), 2.98 - 2.85 (m, 1H), 2.79 - 2.63 (m, 2H), 2.41 - 2.24 (m, 2H), 1.99 - 1.69 (m, 3H), 1.66 - 0.97 (m, 18H), 0.95 (d, *J*=7.0 Hz, 3H), 0.90 (d, *J*=6.1 Hz, 3H), 0.77 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 938.5 (M^++1).

Preparation of Compound 5242 and Compound 5243



Compound 5242



Compound 5243

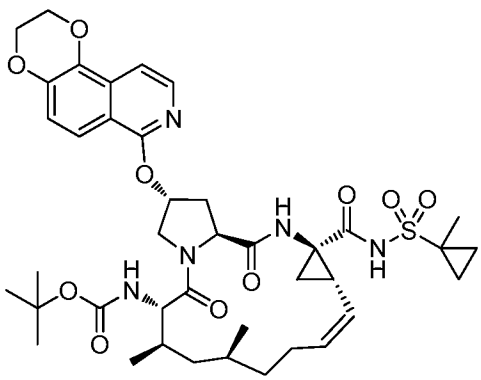
Compounds 5242 and 5243 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5242: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 942.1 (M^++1).

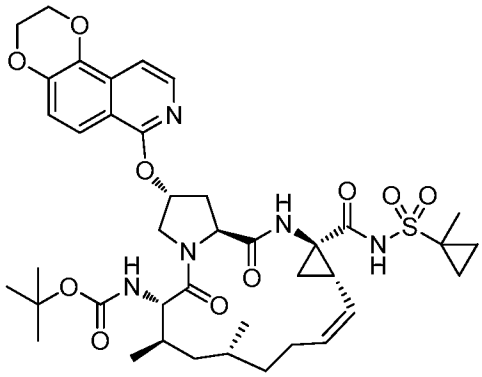
Compound 5243: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (br. s., 1H), 8.96 (br. s., 1H), 8.00 (d, *J*=8.9 Hz, 1H), 7.90 - 7.79 (m, 2H), 7.70 (d, *J*=1.8 Hz, 1H), 7.67 (dd, *J*=8.5, 1.8 Hz, 1H), 7.34 (d, *J*=2.1 Hz, 1H), 7.09 (dd, *J*=9.0, 2.3 Hz, 1H), 7.00 (d, *J*=8.2 Hz, 1H), 5.96 (br.

s., 1H), 5.59 - 5.49 (m, 1H), 5.18 - 5.02 (m, 1H), 4.61 - 4.44 (m, 2H), 4.32 (s, 4H), 3.95 (dd, *J*=11.1, 3.2 Hz, 1H), 3.92 (s, 3H), 3.74 (dd, *J*=10.4, 8.2 Hz, 1H), 2.98 - 2.87 (m, 1H), 2.77 - 2.63 (m, 2H), 2.42 - 2.25 (m, 2H), 1.97 - 1.81 (m, 2H), 1.78 - 1.68 (m, 1H), 1.64 - 0.85 (m, 21H), 0.76 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 942.0 (M^++1).

Preparation of Compound 5244 and Compound 5245



Compound 5244



Compound 5245

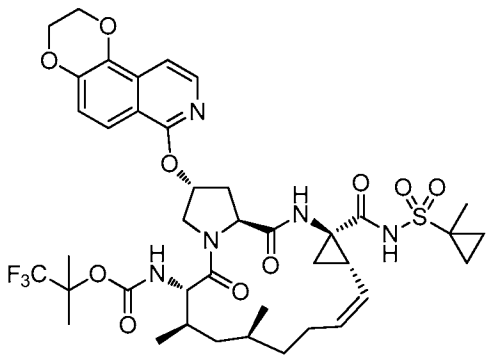
Compounds 5244 and 5245 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5244: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 796.7 (M^++1).

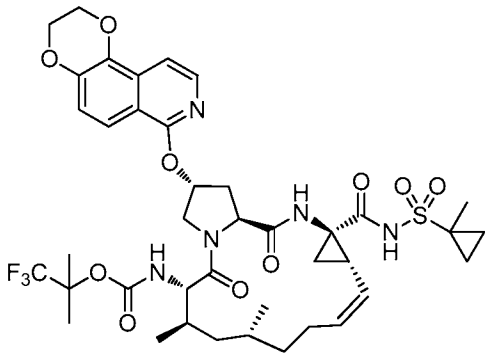
Compound 5245: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.10 (br. s., 1H), 7.96 (d, *J*=6.1 Hz, 1H), 7.66 (d, *J*=8.9 Hz, 1H), 7.37 (d, *J*=6.1 Hz, 1H), 7.16 (d, *J*=7.6 Hz, 1H), 7.08 (d, *J*=8.9 Hz, 1H), 5.81 (br. s., 1H), 5.58 - 5.46 (m, 1H), 5.08 - 4.92 (m, 1H), 4.58 (d, *J*=10.4 Hz, 1H), 4.50 - 4.34 (m, 5H), 3.90 (dd, *J*=11.1, 3.2 Hz, 1H), 3.70 (dd, *J*=10.5, 8.7 Hz, 1H), 2.74 - 2.54 (m,

2H), 2.40 - 2.24 (m, 2H), 1.96 - 1.03 (m, 24H), 0.93 (d, *J*=7.0 Hz, 3H), 0.88 (d, *J*=6.4 Hz, 3H), 0.72 (t, *J*=11.7 Hz, 1H); MS: MS *m/z* 796.7 (M^++1).

Preparation of Compound 5246 and Compound 5247



Compound 5246



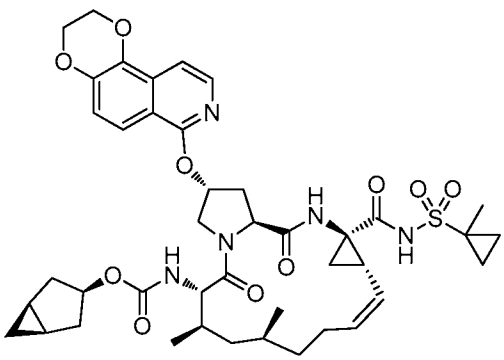
Compound 5247

Compounds 5246 and 5247 were prepared by one of the general procedures described above:

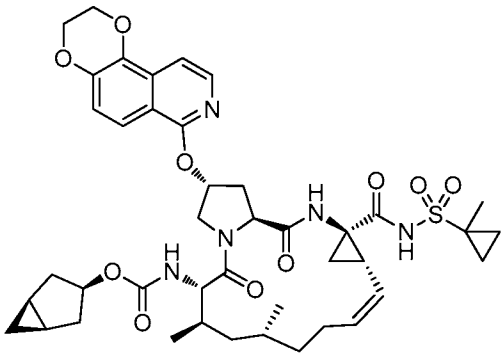
Compound 5246: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 850.7 (M^++1).

Compound 5247: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.15 (br. s., 1H), 7.97 (d, *J*=6.1 Hz, 1H), 7.82 (d, *J*=7.9 Hz, 1H), 7.63 (d, *J*=8.9 Hz, 1H), 7.38 (d, *J*=6.1 Hz, 1H), 7.13 (d, *J*=8.9 Hz, 1H), 5.82 (br. s., 1H), 5.59 - 5.48 (m, 1H), 5.04 - 4.93 (m, 1H), 4.59 - 4.48 (m, 2H), 4.48 - 4.32 (m, 4H), 3.91 (dd, *J*=11.1, 3.2 Hz, 1H), 3.69 (dd, *J*=10.5, 8.1 Hz, 1H), 2.72 - 2.57 (m, 2H), 2.40 - 2.25 (m, 2H), 1.95 - 1.78 (m, 2H), 1.76 - 1.04 (m, 17H), 0.98 - 0.84 (m, 8H), 0.75 (t, *J*=11.9 Hz, 1H); MS: MS *m/z* 850.7 (M^++1).

Preparation of Compound 5248 and Compound 5249



Compound 5248



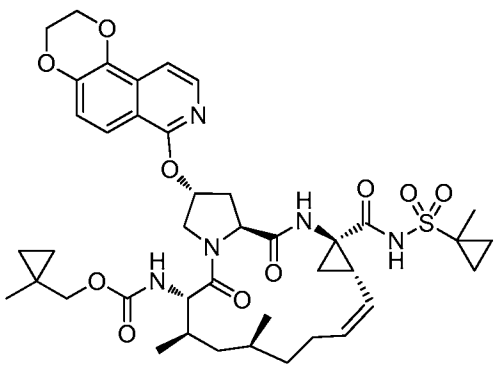
Compound 5249

Compounds 5248 and 5249 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

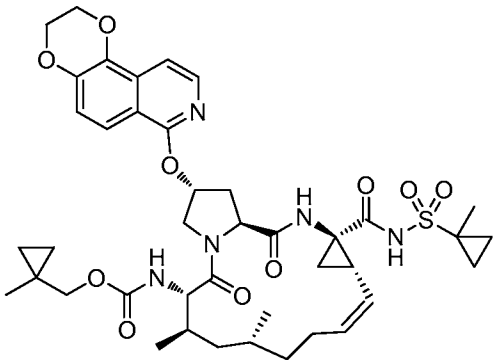
Compound 5248: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 820.7 (M^++1).

Compound 5249: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.07 (br. s., 1H), 7.97 (d, *J*=5.8 Hz, 1H), 7.64 (d, *J*=9.2 Hz, 1H), 7.42 - 7.35 (m, 2H), 7.15 (d, *J*=9.2 Hz, 1H), 5.83 (br. s., 1H), 5.60 - 5.44 (m, 1H), 5.12 - 4.92 (m, 1H), 4.62 (t, *J*=6.6 Hz, 1H), 4.52 - 4.32 (m, 5H), 3.93 (dd, *J*=11.1, 3.2 Hz, 1H), 3.75 (dd, *J*=10.5, 9.0 Hz, 1H), 2.76 - 2.54 (m, 2H), 2.35 - 2.22 (m, 2H), 2.03 - 1.07 (m, 20H), 0.99 - 0.82 (m, 8H), 0.72 (t, *J*=12.4 Hz, 1H), 0.36 (d, *J*=4.9 Hz, 2H); MS: MS *m/z* 820.7 (M^++1).

Preparation of Compound 5250 and Compound 5251



Compound 5250



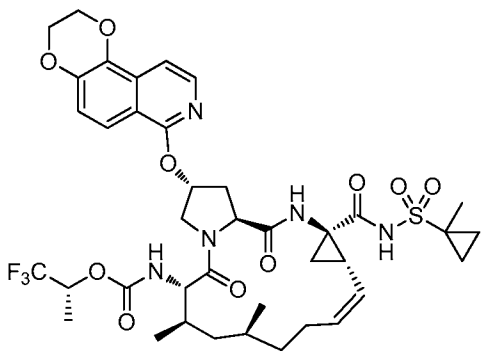
Compound 5251

Compounds 5250 and 5251 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

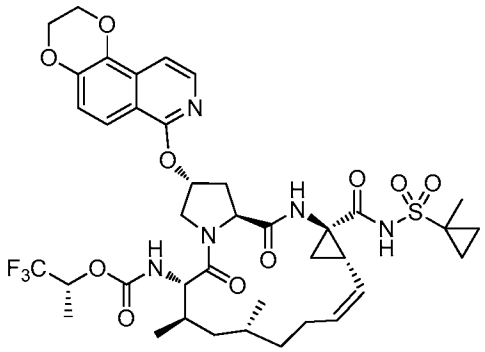
Compound 5250: (1-methylcyclopropyl)methyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 808.7 (M^++1).

Compound 5251: (1-methylcyclopropyl)methyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.09 (br. s., 1H), 7.96 (d, *J*=6.1 Hz, 1H), 7.63 (d, *J*=9.2 Hz, 1H), 7.50 (d, *J*=7.3 Hz, 1H), 7.38 (d, *J*=5.8 Hz, 1H), 7.12 (d, *J*=8.9 Hz, 1H), 5.83 (br. s., 1H), 5.58 - 5.48 (m, 1H), 5.06 - 4.94 (m, 1H), 4.58 - 4.35 (m, 6H), 3.94 (dd, *J*=11.1, 3.2 Hz, 1H), 3.76 (dd, *J*=10.7, 8.5 Hz, 1H), 3.46 - 3.39 (m, 2H), 2.75 - 2.54 (m, 2H), 2.39 - 2.23 (m, 2H), 1.97 - 1.79 (m, 2H), 1.74 - 0.82 (m, 22H), 0.74 (t, *J*=12.3 Hz, 1H), 0.31 - 0.25 (m, 1H), 0.24 - 0.15 (m, 3H); MS: MS *m/z* 808.7 (M^++1).

Preparation of Compound 5252 and Compound 5253



Compound 5252



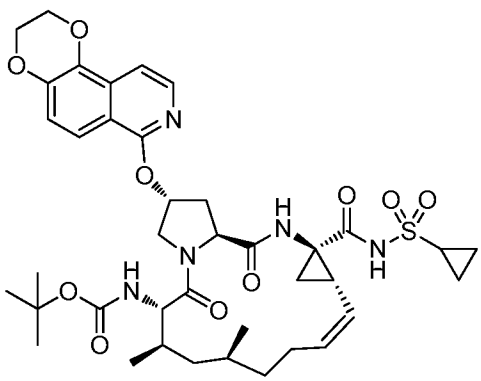
Compound 5253

Compounds 5252 and 5253 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

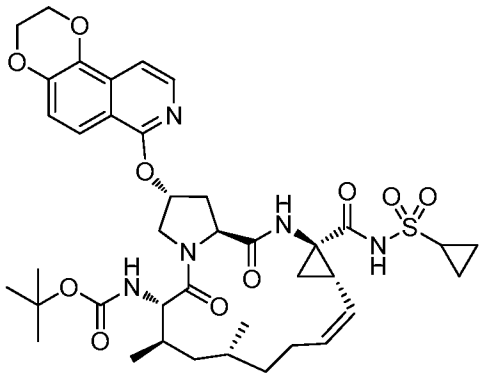
Compound 5252: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 836.7 (M^++1).

Compound 5253: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.10 (br. s., 1H), 8.08 (d, *J*=7.9 Hz, 1H), 7.97 (d, *J*=5.8 Hz, 1H), 7.60 (d, *J*=9.2 Hz, 1H), 7.39 (d, *J*=6.1 Hz, 1H), 7.06 (d, *J*=8.9 Hz, 1H), 5.83 (br. s., 1H), 5.61 - 5.46 (m, 1H), 5.09 - 4.93 (m, 1H), 4.77 - 4.67 (m, 1H), 4.58 - 4.32 (m, 6H), 3.94 (dd, *J*=11.1, 3.2 Hz, 1H), 3.77 (dd, *J*=10.8, 8.1 Hz, 1H), 2.72 - 2.56 (m, 2H), 2.36 - 2.25 (m, 2H), 1.96 - 1.81 (m, 2H), 1.74 - 0.85 (m, 22H), 0.77 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 836.7 (M^++1).

Preparation of Compound 5254 and Compound 5255



Compound 5254



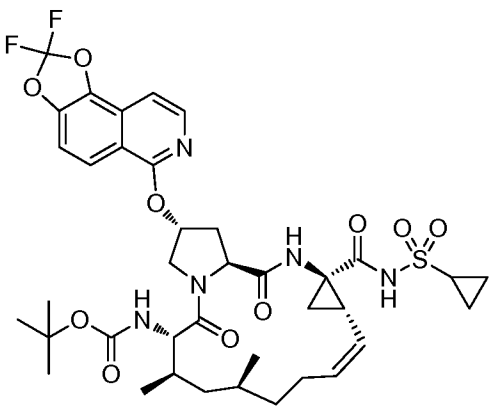
Compound 5255

Compounds 5254 and 5255 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

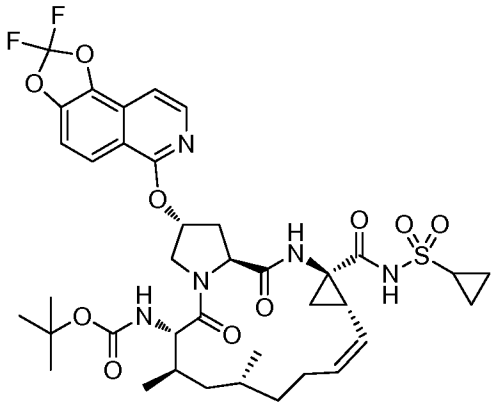
Compound 5254: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 796.7 (M^++1).

Compound 5255: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.10 (br. s., 1H), 7.96 (d, *J*=6.1 Hz, 1H), 7.66 (d, *J*=8.9 Hz, 1H), 7.37 (d, *J*=6.1 Hz, 1H), 7.16 (d, *J*=7.6 Hz, 1H), 7.08 (d, *J*=8.9 Hz, 1H), 5.81 (br. s., 1H), 5.58 - 5.46 (m, 1H), 5.08 - 4.92 (m, 1H), 4.58 (d, *J*=10.4 Hz, 1H), 4.50 - 4.34 (m, 5H), 3.90 (dd, *J*=11.1, 3.2 Hz, 1H), 3.70 (dd, *J*=10.5, 8.7 Hz, 1H), 2.74 - 2.54 (m, 2H), 2.40 - 2.24 (m, 2H), 1.96 - 1.03 (m, 24H), 0.93 (d, *J*=7.0 Hz, 3H), 0.88 (d, *J*=6.4 Hz, 3H), 0.72 (t, *J*=11.7 Hz, 1H); MS: MS *m/z* 796.7 (M^++1).

Preparation of Compound 5256 and Compound 5257



Compound 5256



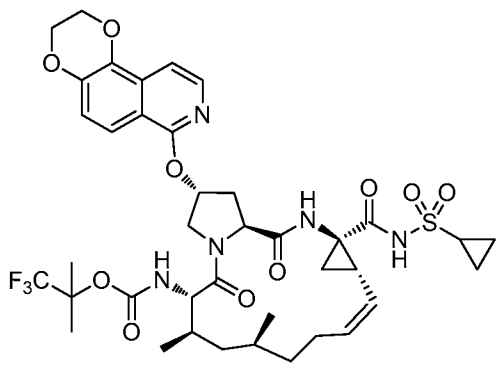
Compound 5257

Compounds 5256 and 5257 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

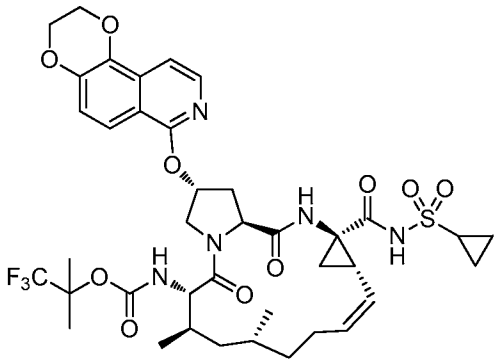
Compound 5256: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,2-difluoro-[1,3]dioxolo[4,5-f]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 804.5 (M^++1).

Compound 5257: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,2-difluoro-[1,3]dioxolo[4,5-f]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.20 (br. s., 1H), 9.03 (br. s., 1H), 8.17 (d, *J*=5.8 Hz, 1H), 8.06 (d, *J*=8.9 Hz, 1H), 7.71 (d, *J*=9.2 Hz, 1H), 7.41 (d, *J*=5.8 Hz, 1H), 7.15 (d, *J*=7.3 Hz, 1H), 5.85 (br. s., 1H), 5.61 - 5.46 (m, 1H), 5.10 - 4.98 (m, 1H), 4.65 (d, *J*=11.6 Hz, 1H), 4.58 - 4.45 (m, 1H), 3.88 (dd, *J*=11.6, 3.1 Hz, 1H), 3.62 (dd, *J*=10.4, 8.2 Hz, 1H), 2.98 - 2.88 (m, 1H), 2.72 - 2.60 (m, 2H), 2.40 - 2.24 (m, 2H), 1.95 - 1.85 (m, 1H), 1.84 - 1.75 (m, 1H), 1.73 - 1.65 (m, 1H), 1.64 - 1.52 (m, 2H), 1.49 - 1.31 (m, 2H), 1.23 - 0.83 (m, 20H), 0.72 (t, *J*=12.7 Hz, 1H); MS: MS *m/z* 804.6 (M^++1).

Preparation of Compound 5258 and Compound 5259



Compound 5258



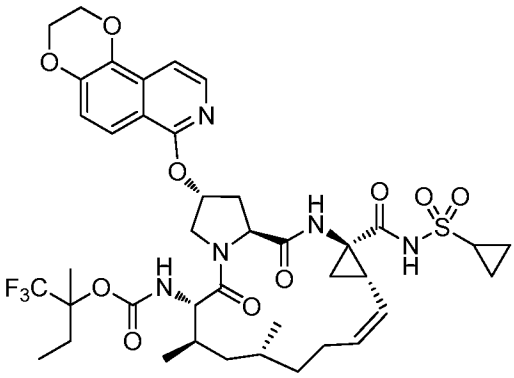
Compound 5259

Compounds 5258 and 5259 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5258: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 836.6 (M^++1).

Compound 5259: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (br. s., 1H), 9.01 (br. s., 1H), 7.98 (d, *J*=6.1 Hz, 1H), 7.82 (d, *J*=7.6 Hz, 1H), 7.63 (d, *J*=8.9 Hz, 1H), 7.38 (d, *J*=5.8 Hz, 1H), 7.12 (d, *J*=8.9 Hz, 1H), 5.81 (br. s., 1H), 5.59 - 5.48 (m, 1H), 5.11 - 5.00 (m, 1H), 4.61 - 4.30 (m, 6H), 3.89 (dd, *J*=11.3, 3.1 Hz, 1H), 3.69 (dd, *J*=10.7, 8.2 Hz, 1H), 2.95 - 2.87 (m, 1H), 2.71 - 2.57 (m, 2H), 2.31 (ddd, *J*=13.7, 10.2, 3.8 Hz, 2H), 1.95 - 1.79 (m, 2H), 1.75 - 1.67 (m, 1H), 1.65 - 1.53 (m, 2H), 1.47 - 0.84 (m, 19H), 0.74 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 836.6 (M^++1).

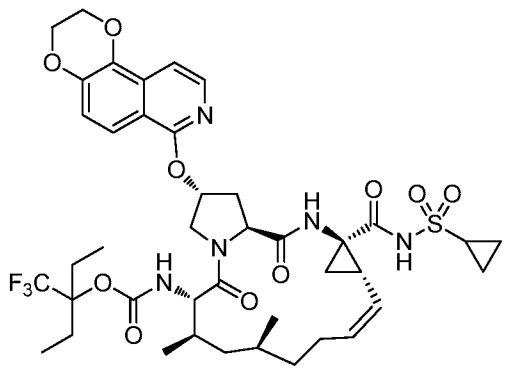
Preparation of Compound 5260



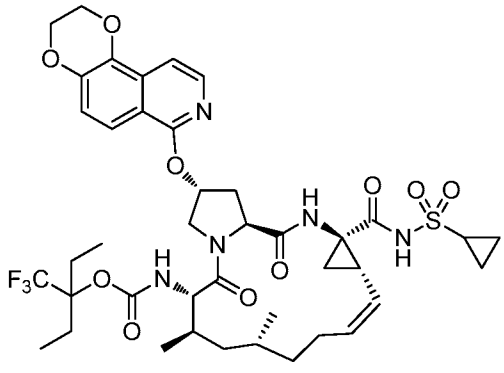
Compound 5260

Compound 5260 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117: Compound 5260: 1,1,1-trifluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 850.7 (M^++1).

Preparation of Compound 5261 and Compound 5262



Compound 5261



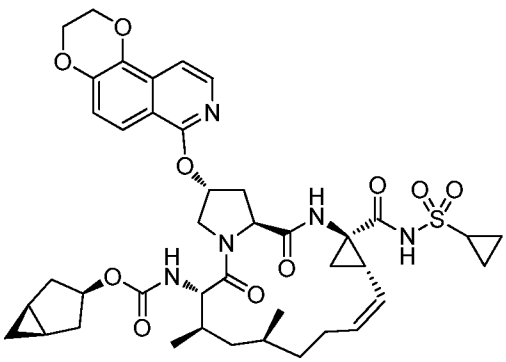
Compound 5262

Compounds 5261 and 5262 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

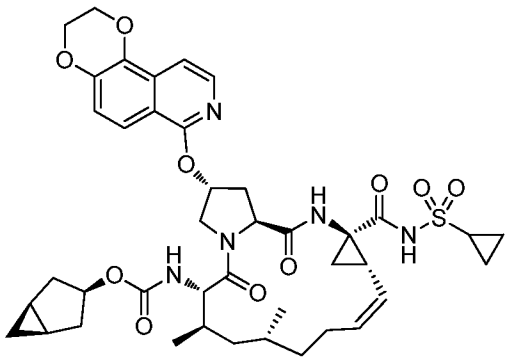
Compound 5261: 3-(trifluoromethyl)pentan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 864.7 (M^++1).

Compound 5262: 3-(trifluoromethyl)pentan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (br. s., 1H), 9.03 (br. s., 1H), 7.97 (d, *J*=6.1 Hz, 1H), 7.86 (d, *J*=7.9 Hz, 1H), 7.59 (d, *J*=9.2 Hz, 1H), 7.38 (d, *J*=6.1 Hz, 1H), 7.12 (d, *J*=8.9 Hz, 1H), 5.80 (br. s., 1H), 5.62 - 5.47 (m, 1H), 5.15 - 4.98 (m, 1H), 4.58 - 4.34 (m, 6H), 3.93 (dd, *J*=11.1, 3.4 Hz, 1H), 3.74 (dd, *J*=10.7, 8.5 Hz, 1H), 2.96 - 2.87 (m, 1H), 2.73 - 2.57 (m, 2H), 2.37 - 2.25 (m, 2H), 1.95 - 0.86 (m, 22H), 0.77 (t, *J*=7.5 Hz, 4H), 0.60 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 864.6 (M^++1).

Preparation of Compound 5263 and Compound 5264



Compound 5263



Compound 5264

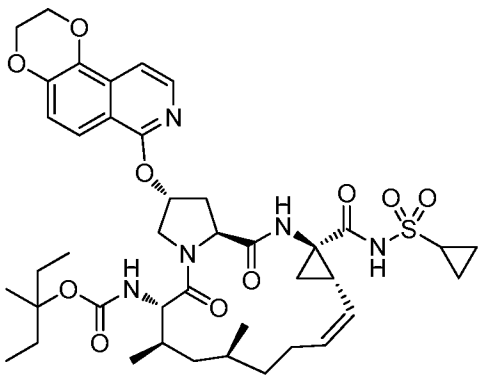
Compounds 5263 and 5264 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5263: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-5,16-dioxo-

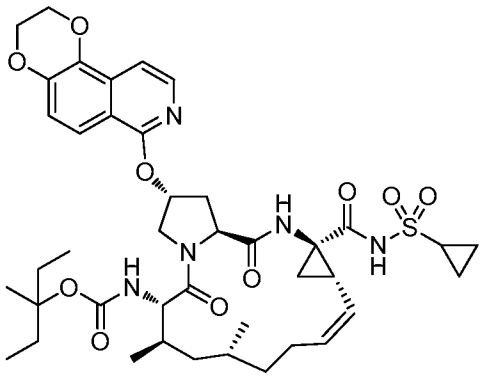
1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 806.7 (M^++1).

Compound 5264: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (br. s., 1H), 8.95 (br. s., 1H), 7.97 (d, *J*=6.1 Hz, 1H), 7.64 (d, *J*=9.2 Hz, 1H), 7.43 - 7.35 (m, 2H), 7.14 (d, *J*=8.9 Hz, 1H), 5.82 (br. s., 1H), 5.59 - 5.45 (m, 1H), 5.18 - 4.99 (m, 1H), 4.64 (t, *J*=6.7 Hz, 1H), 4.52 - 4.33 (m, 6H), 3.91 (dd, *J*=11.3, 3.4 Hz, 1H), 3.75 (dd, *J*=10.5, 9.0 Hz, 1H), 2.96 - 2.85 (m, 1H), 2.72 - 2.54 (m, 2H), 2.37 - 2.21 (m, 2H), 2.01 - 1.89 (m, 2H), 1.87 - 1.76 (m, 2H), 1.75 - 0.82 (m, 20H), 0.71 (t, *J*=12.4 Hz, 1H), 0.40 - 0.31 (m, 2H); MS: MS *m/z* 806.7 (M^++1).

Preparation of Compound 5265 and Compound 5266



Compound 5265



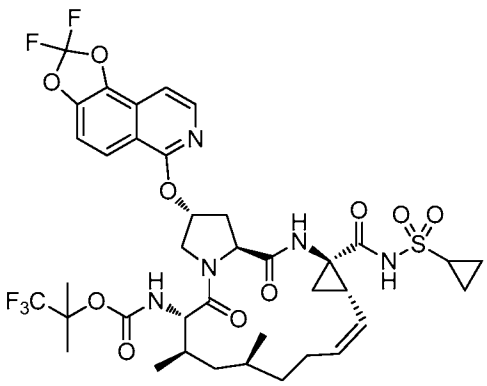
Compound 5266

Compounds 5265 and 5266 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

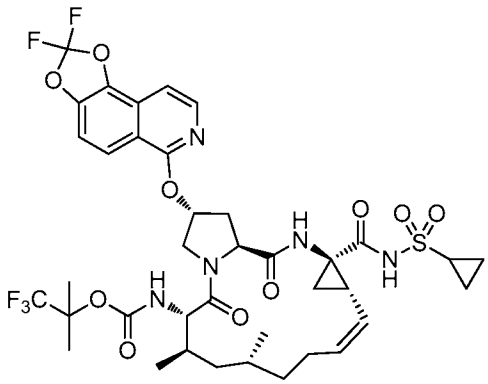
Compound 5265: 3-methylpentan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 810.7 (M^++1).

Compound 5266: 3-methylpentan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (br. s., 1H), 8.99 (br. s., 1H), 7.96 (d, *J*=6.1 Hz, 1H), 7.63 (d, *J*=9.2 Hz, 1H), 7.38 (d, *J*=6.1 Hz, 1H), 7.17 (d, *J*=8.2 Hz, 1H), 7.09 (d, *J*=8.9 Hz, 1H), 5.80 (br. s., 1H), 5.59 - 5.47 (m, 1H), 5.13 - 4.97 (m, 1H), 4.54 (d, *J*=11.0 Hz, 1H), 4.48 - 4.33 (m, 5H), 3.90 (dd, *J*=11.3, 3.4 Hz, 1H), 3.72 (dd, *J*=10.4, 8.9 Hz, 1H), 2.94 - 2.85 (m, 1H), 2.73 - 2.55 (m, 2H), 2.37 - 2.23 (m, 2H), 1.97 - 1.78 (m, 2H), 1.76 - 1.65 (m, 1H), 1.65 - 0.83 (m, 22H), 0.78 - 0.59 (m, 7H); MS: MS *m/z* 810.7 (M^++1).

Preparation of Compound 5267and Compound 5268



Compound 5267



Compound 5268

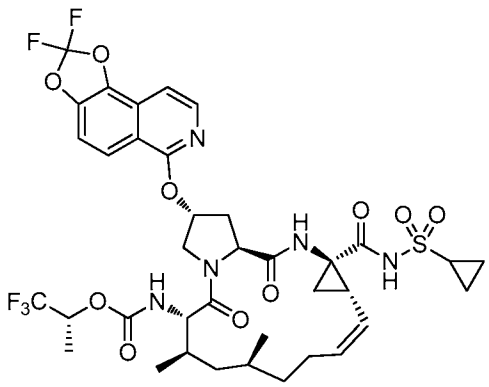
Compounds 5267 and 5268 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5267: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,2-difluoro-[1,3]dioxolo[4,5-f]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 858.7 (M^++1).

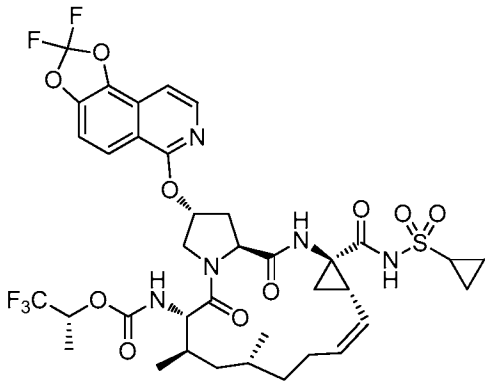
Compound 5268: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,2-difluoro-[1,3]dioxolo[4,5-f]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-

a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (br. s., 1H), 9.05 (br. s., 1H), 8.18 (d, *J*=5.8 Hz, 1H), 8.05 (d, *J*=9.2 Hz, 1H), 7.81 (d, *J*=7.3 Hz, 1H), 7.76 (d, *J*=9.2 Hz, 1H), 7.42 (d, *J*=5.8 Hz, 1H), 5.85 (br. s., 1H), 5.60 - 5.46 (m, 1H), 5.13 - 4.99 (m, 1H), 4.63 - 4.48 (m, 2H), 3.89 (dd, *J*=11.3, 3.1 Hz, 1H), 3.64 (dd, *J*=10.5, 7.8 Hz, 1H), 2.91 (s, 1H), 2.71 - 2.58 (m, 2H), 2.43 - 2.21 (m, 2H), 1.95 - 0.90 (m, 21H), 0.88 (d, *J*=6.1 Hz, 3H), 0.74 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 858.7 (M^++1).

Preparation of Compound 5269 and Compound 5270



Compound 5269



Compound 5270

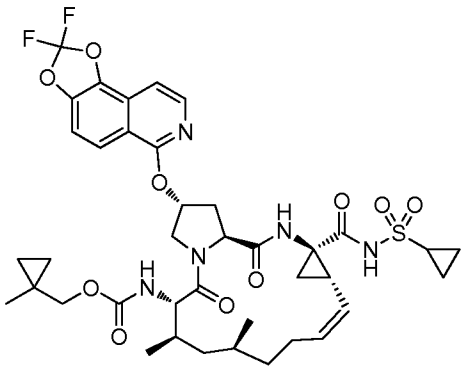
Compounds 5269 and 5270 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5269: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,2-difluoro-[1,3]dioxolo[4,5-f]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 844.6 (M^++1).

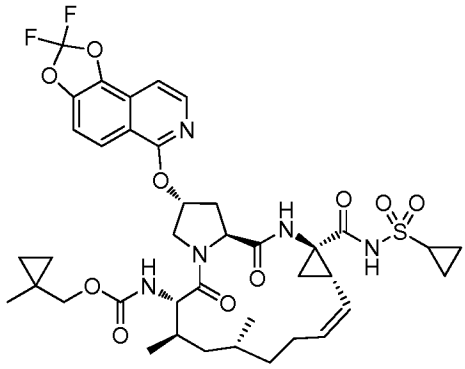
Compound 5270: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,2-difluoro-[1,3]dioxolo[4,5-f]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.20 (br. s., 1H), 9.04 (br. s., 1H), 8.16 (d, *J*=5.8 Hz, 1H), 8.06 - 7.98 (m, 2H), 7.70

(d, *J*=8.9 Hz, 1H), 7.42 (d, *J*=5.8 Hz, 1H), 5.85 (br. s., 1H), 5.59 - 5.47 (m, 1H), 5.12 - 5.00 (m, 1H), 4.65 - 4.49 (m, 2H), 4.31 (quin, *J*=6.8 Hz, 1H), 3.90 (dd, *J*=11.3, 3.1 Hz, 1H), 3.69 (dd, *J*=10.7, 8.2 Hz, 1H), 2.99 - 2.89 (m, 1H), 2.70 - 2.60 (m, 2H), 2.41 - 2.32 (m, 1H), 2.32 - 2.19 (m, 1H), 1.99 - 1.77 (m, 2H), 1.71 - 1.52 (m, 3H), 1.48 - 1.31 (m, 2H), 1.21 - 0.95 (m, 8H), 0.93 (d, *J*=7.0 Hz, 3H), 0.87 (d, *J*=6.4 Hz, 3H), 0.74 (t, *J*=11.9 Hz, 1H); MS: MS *m/z* 844.6 (M^++1).

Preparation of Compound 5271 and Compound 5272



Compound 5271



Compound 5272

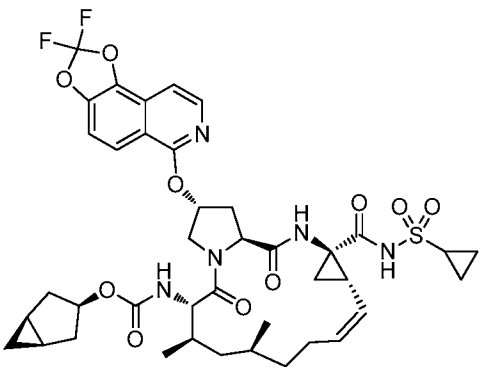
Compounds 5271 and 5272 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5271: (1-methylcyclopropyl)methyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,2-difluoro-[1,3]dioxolo[4,5-f]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 816.7 (M^++1).

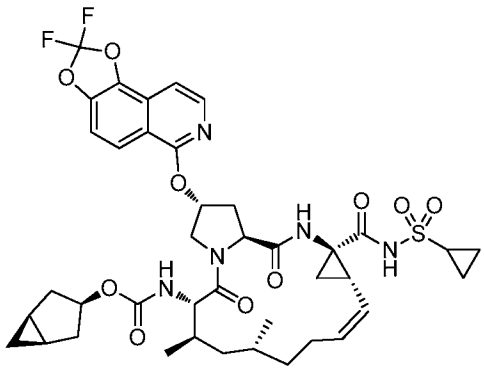
Compound 5272: (1-methylcyclopropyl)methyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,2-difluoro-[1,3]dioxolo[4,5-f]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.20 (br. s., 1H), 9.00 (br. s., 1H), 8.16 (d, *J*=6.1 Hz, 1H), 8.04 (d, *J*=9.2 Hz, 1H), 7.75 (d, *J*=8.9 Hz, 1H), 7.46 (d, *J*=7.6 Hz, 1H), 7.42 (d, *J*=5.8 Hz, 1H), 5.86 (br. s., 1H), 5.59 - 5.45 (m, 1H), 5.14 - 4.95 (m, 1H), 4.59 (d, *J*=11.3 Hz, 1H), 4.52 (t, *J*=8.1

Hz, 1H), 3.90 (dd, *J*=11.3, 3.1 Hz, 1H), 3.68 (dd, *J*=10.5, 8.4 Hz, 1H), 3.30 - 3.12 (m, 2H), 2.98 - 2.87 (m, 1H), 2.72 - 2.57 (m, 2H), 2.40 - 2.31 (m, 1H), 2.31 - 2.20 (m, 1H), 1.97 - 1.87 (m, 1H), 1.87 - 1.76 (m, 1H), 1.73 - 1.51 (m, 3H), 1.48 - 1.30 (m, 2H), 1.22 - 0.77 (m, 14H), 0.73 (t, *J*=12.1 Hz, 1H), 0.23 - 0.04 (m, 4H); MS: MS *m/z* 816.7 (M^++1).

Preparation of Compound 5273 and Compound 5274



Compound 5273



Compound 5274

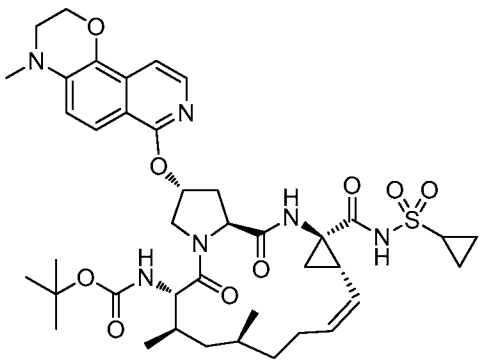
Compounds 5273 and 5274 were were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5273: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,2-difluoro-[1,3]dioxolo[4,5-f]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 828.6 (M^++1).

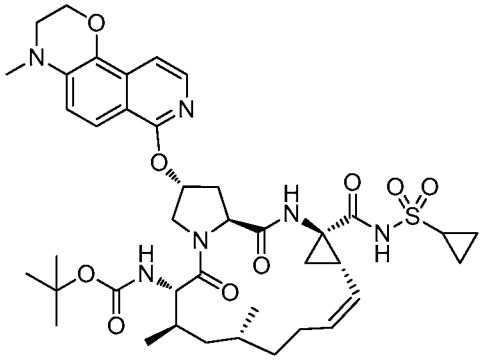
Compound 5274: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,2-difluoro-[1,3]dioxolo[4,5-f]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (br. s., 1H), 8.98 (br. s., 1H), 8.16 (d, *J*=5.8 Hz, 1H), 8.06 (d, *J*=8.9 Hz, 1H), 7.78 (d, *J*=8.9 Hz, 1H), 7.43 (d, *J*=6.1 Hz, 1H), 7.36 (d, *J*=7.9 Hz, 1H), 5.87 (br. s., 1H), 5.57 - 5.47 (m, 1H), 5.12 - 4.99 (m, 1H), 4.58 - 4.42 (m, 3H), 3.91 (dd, *J*=11.3, 3.1 Hz, 1H), 3.69 (dd, *J*=10.7, 8.5 Hz, 1H), 2.91 (s, 1H), 2.72 - 2.59 (m, 2H), 2.41 -

2.21 (m, 2H), 2.00 - 1.75 (m, 3H), 1.72 - 0.87 (m, 18H), 0.85 (d, *J*=6.4 Hz, 3H), 0.72 (t, *J*=11.7 Hz, 1H), 0.38 - 0.24 (m, 2H); MS: MS *m/z* 828.5 (M^++1).

Preparation of Compound 5275 and Compound 5276



Compound 5275



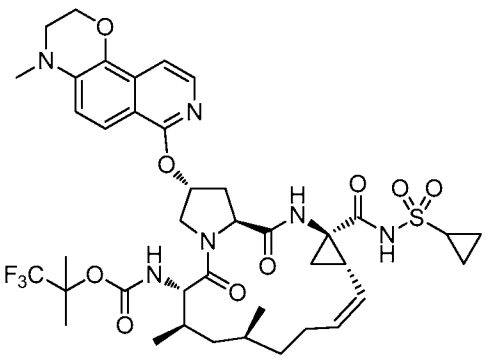
Compound 5276

Compounds 5275 and 5276 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

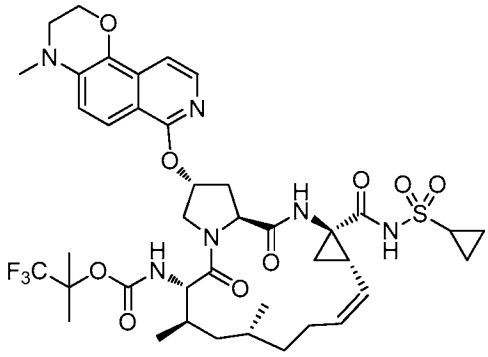
Compound 5275: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 795.6 (M^++1).

Compound 5276: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (br. s., 1H), 8.97 (br. s., 1H), 7.81 (d, *J*=6.1 Hz, 1H), 7.62 (d, *J*=9.2 Hz, 1H), 7.24 (d, *J*=6.1 Hz, 1H), 7.17 (d, *J*=8.2 Hz, 1H), 7.05 (d, *J*=9.2 Hz, 1H), 5.78 (br. s., 1H), 5.59 - 5.45 (m, 1H), 5.13 - 4.99 (m, 1H), 4.53 (d, *J*=11.6 Hz, 1H), 4.45 - 4.33 (m, 3H), 3.88 (dd, *J*=11.3, 3.4 Hz, 1H), 3.73 (dd, *J*=9.9, 9.0 Hz, 1H), 3.43 - 3.38 (m, 2H), 2.98 (s, 3H), 2.95 - 2.88 (m, 1H), 2.73 - 2.64 (m, 1H), 2.62 - 2.54 (m, 1H), 2.36 - 2.22 (m, 2H), 1.98 - 0.95 (m, 21H), 0.93 (d, *J*=6.7 Hz, 3H), 0.88 (d, *J*=6.1 Hz, 3H), 0.72 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 795.6 (M^++1).

Preparation of Compound 5277 and Compound 5278



Compound 5277



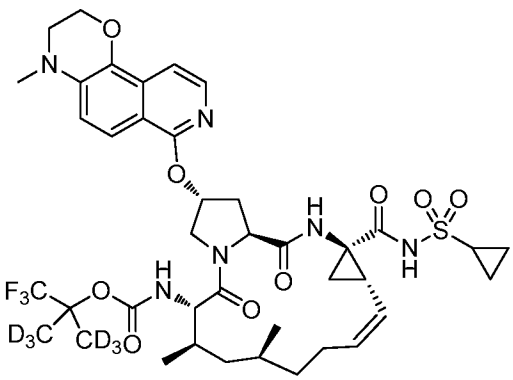
Compound 5278

Compounds 5277 and 5278 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

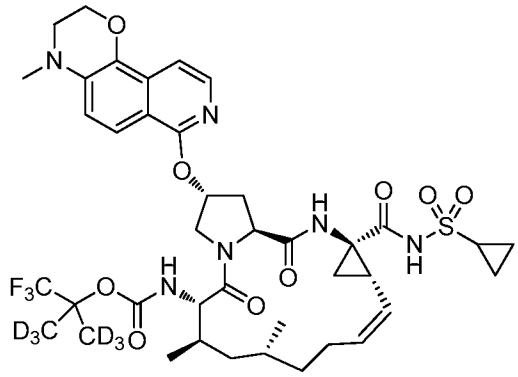
Compound 5277: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 849.6 (M^++1).

Compound 5278: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (br. s., 1H), 9.00 (br. s., 1H), 7.85 - 7.77 (m, 2H), 7.59 (d, *J*=8.9 Hz, 1H), 7.25 (d, *J*=6.1 Hz, 1H), 7.08 (d, *J*=9.2 Hz, 1H), 5.79 (br. s., 1H), 5.58 - 5.44 (m, 1H), 5.17 - 5.02 (m, 1H), 4.51 - 4.43 (m, 2H), 4.42 - 4.30 (m, 2H), 3.88 (dd, *J*=11.4, 3.2 Hz, 1H), 3.71 (dd, *J*=10.7, 8.2 Hz, 1H), 3.46 - 3.37 (m, 2H), 2.98 (s, 3H), 2.94 - 2.86 (m, 1H), 2.72 - 2.54 (m, 2H), 2.36 - 2.23 (m, 2H), 1.95 - 1.80 (m, 2H), 1.77 - 1.67 (m, 1H), 1.63 - 0.96 (m, 15H), 0.93 (d, *J*=7.0 Hz, 3H), 0.88 (d, *J*=6.4 Hz, 3H), 0.72 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 849.5 (M^++1).

Preparation of Compound 5279 and Compound 5280



Compound 5279



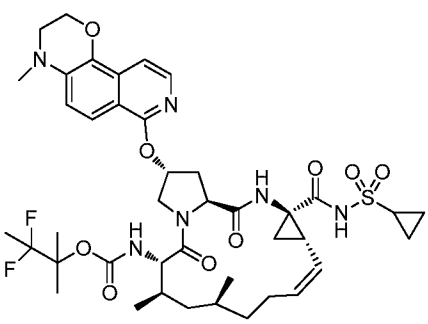
Compound 5280

Compounds 5279 and 5280 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

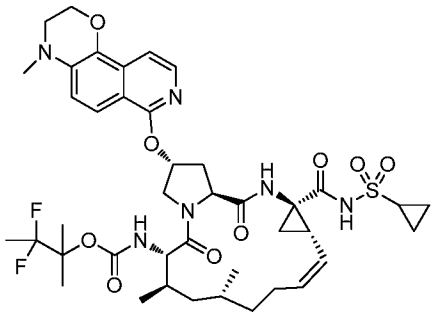
Compound 5279: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate MS: MS *m/z* 855.6 (M^++1).

Compound 5280: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (br. s., 1H), 9.01 (br. s., 1H), 7.85 - 7.77 (m, 2H), 7.59 (d, *J*=9.2 Hz, 1H), 7.25 (d, *J*=6.1 Hz, 1H), 7.08 (d, *J*=9.2 Hz, 1H), 5.79 (br. s., 1H), 5.61 - 5.48 (m, 1H), 5.11 - 4.99 (m, 1H), 4.51 - 4.43 (m, 2H), 4.42 - 4.31 (m, 2H), 3.88 (dd, *J*=11.3, 3.4 Hz, 1H), 3.71 (dd, *J*=10.5, 8.4 Hz, 1H), 3.47 - 3.37 (m, 2H), 2.98 (s, 3H), 2.91 (s, 1H), 2.73 - 2.55 (m, 2H), 2.36 - 2.20 (m, 2H), 1.94 - 1.78 (m, 2H), 1.76 - 1.67 (m, 1H), 1.64 - 0.95 (m, 9H), 0.94 (d, *J*=6.7 Hz, 3H), 0.88 (d, *J*=6.4 Hz, 3H), 0.73 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 855.6 (M^++1).

Preparation of Compound 5281 and Compound 5282



Compound 5281



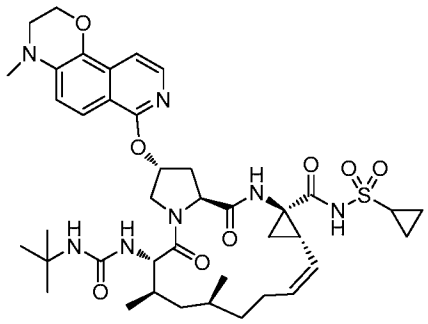
Compound 5282

Compounds 5281 and 5282 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

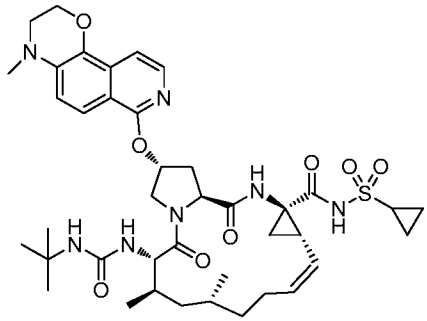
Compound 5281: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 845.6 (M^++1).

Compound 5282: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (br. s., 1H), 8.98 (br. s., 1H), 7.82 (d, *J*=6.1 Hz, 1H), 7.60 (m, 2H), 7.25 (d, *J*=6.1 Hz, 1H), 7.07 (d, *J*=9.2 Hz, 1H), 5.79 (m 1H), 5.52 (m 1H), 5.06 (m, 1H), 4.46 (d, *J*=7.9 Hz, 2H), 4.42 - 4.23 (m, 2H), 3.99 - 3.81 (m, 1H), 3.72 (dd, *J*=10.5, 8.7 Hz, 1H), 3.40 (m, 2H), 2.90-2.35(m, 3H), 2.32 - 2.24 (m, 2H), 1.97 - 1.07 (m, 24H), 0.97 - 0.80 (m, 6H), 0.73 (m, 1H); MS: MS *m/z* 845.6 (M^++1).

Preparation of Compound 5283 and Compound 5284



Compound 5283



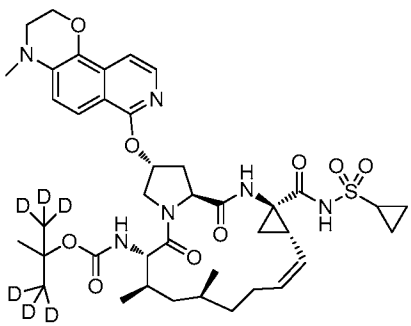
Compound 5284

Compounds 5283 and 5284 were were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

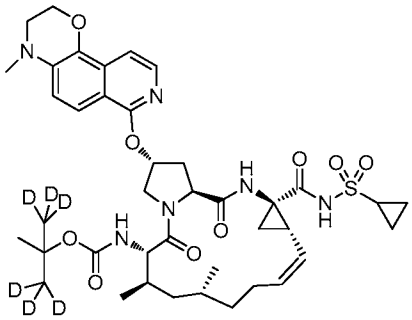
Compound 5283: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-N-(cyclopropylsulfonyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 794.7 (M^++1).

Compound 5284: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-N-(cyclopropylsulfonyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.82 - 7.66 (m, 2H), 7.32 (d, *J*=6.1 Hz, 1H), 7.00 (d, *J*=9.2 Hz, 1H), 5.81 (br. s., 1H), 5.44 (td, *J*=10.1, 5.6 Hz, 1H), 5.06 (t, *J*=10.1 Hz, 1H), 4.71 (d, *J*=11.3 Hz, 1H), 4.55 (dd, *J*=9.8, 7.3 Hz, 1H), 4.45 - 4.33 (m, 2H), 4.09 - 3.95 (m, 2H), 3.41 (dd, *J*=5.0, 3.5 Hz, 2H), 2.94 - 2.84 (m, 3H), 2.74 - 2.54 (m, 2H), 2.47 - 2.25 (m, 2H), 1.96 (s, 3H), 1.83 - 1.65 (m, 4H), 1.48 (dd, *J*=9.5, 5.5 Hz, 1H), 1.35 - 1.21 (m, 3H), 1.17 (s, 9H), 1.14 - 1.01 (m, 3H), 0.96 (m, 6H), 0.80 (t, *J*=11.7 Hz, 1H); MS: MS *m/z* 794.7 (M^++1).

Preparation of Compound 5285 and Compound 5286



Compound 5285



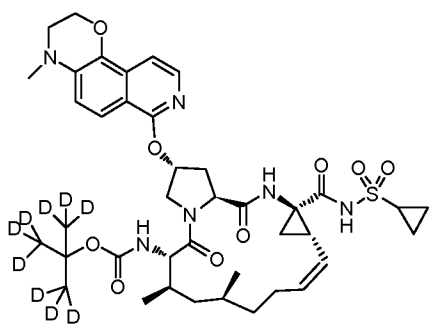
Compound 5286

Compounds 5285 and 5286 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

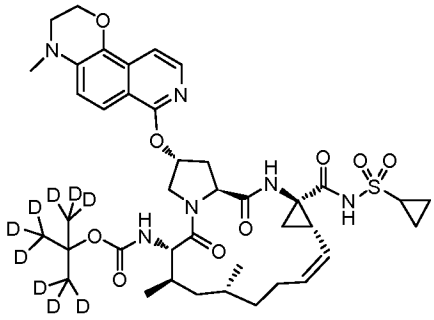
Compound 5285: 1,1,1,3,3,3-hexadeutero-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamateMS: MS *m/z* 801.7 (M^++1).

Compound 5286: 1,1,1,3,3,3-hexadeutero-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (br. s., 1H), 8.96 (br. s., 1H), 7.81 (d, *J*=6.1 Hz, 1H), 7.62 (d, *J*=9.2 Hz, 1H), 7.24 (d, *J*=6.1 Hz, 1H), 7.13 (br. s., 1H), 7.05 (d, *J*=9.2 Hz, 1H), 5.78 (m, 1H), 5.49 (m, 1H), 5.06 (m, 1H), 4.49 (m, 1H), 4.42 - 4.34 (m, 3H), 3.98 - 3.82 (m, 1H), 3.79 - 3.63 (m, 1H), 2.98 9s, 3H), 2.92 - 2.83 (m, 2H), 2.38 - 2.20 (m, 2H), 1.99 – 1.10 (m, 18 H), 1.01 - 0.82 (m, 6H), 0.76 - 0.63 (m, 1H); MS: MS *m/z* 801.7 (M^++1).

Preparation of Compound 5287 and Compound 5288



Compound 5287



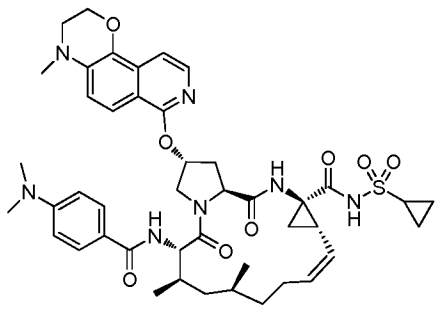
Compound 5288

Compounds 5287 and 5288 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

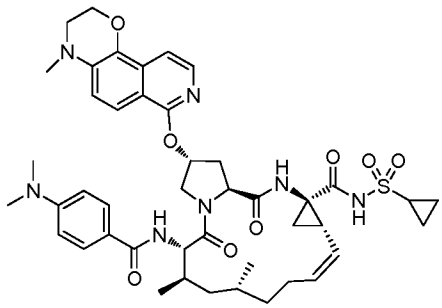
Compound 5287: 1,1,1,3,3,3-hexadeutero-2-(trideuteromethyl)propan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamateMS: MS *m/z* 804.7 (M^++1).

Compound 5288: 1,1,1,3,3,3-hexadeutero-2-(trideuteromethyl)propan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (br. s., 1H), 8.96 (br. s., 1H), 7.81 (d, *J*=6.1 Hz, 1H), 7.62 (d, *J*=8.9 Hz, 1H), 7.24 (d, *J*=6.1 Hz, 1H), 7.13 (br. s., 1H), 7.05 (d, *J*=9.2 Hz, 1H), 5.78 (s 1H), 5.48 (m, 1H), 5.09 (m, 1H), 4.49 (m, 1H), 4.44 - 4.30 (m, 3H), 4.01 - 3.83 (m, 2H), 3.78 - 3.67 (m, 1H), 3.40 (d, *J*=2.7 Hz, 2H), 2.98 (s, 3H), 2.38 - 2.22 (m, 2H), 1.92-1.05 (m, 14 H) , 0.99 - 0.80 (m, 6H), 0.80 - 0.64 (m, 1H); MS: MS *m/z* 804.7 (M^++1).

Preparation of Compound 5289 and Compound 5290



Compound 5289



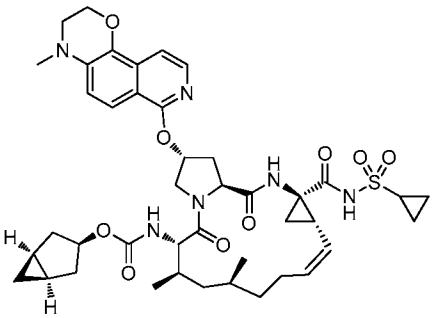
Compound 5290

Compounds 5289 and 5290 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

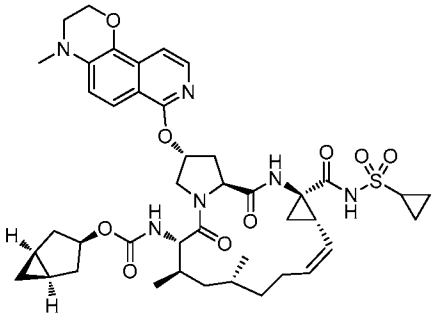
Compound 5289: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(4-(dimethylamino)benzamido)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 842.7 (M^++1).

Compound 5290: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(4-(dimethylamino)benzamido)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (br. s., 1H), 8.96 (br. s., 1H), 8.27 (d, *J*=8.2 Hz, 1H), 7.82 (d, *J*=6.1 Hz, 1H), 7.72 - 7.65 (m, *J*=8.9 Hz, 2H), 7.52 (d, *J*=8.9 Hz, 1H), 7.25 (d, *J*=6.1 Hz, 1H), 6.91 (d, *J*=8.9 Hz, 1H), 6.69 - 6.60 (m, *J*=9.2 Hz, 2H), 5.79 (br. s., 1H), 5.49 (m, 1H), 4.68 (m, 1H), 4.45 - 4.25 (m, 4H), 3.97 (dd, *J*=11.0, 3.7 Hz, 1H), 3.41 (m, 2H), 3.03 - 2.89 (m, 10H), 2.37 - 2.23 (m, 2H), 2.17 - 2.08 (m, 1H), 1.99 (m, 1H), 1.80 (m, 1H), 1.49-1.25 (m, 9H), 0.95 (m, 9H), 0.87 - 0.74 (m, 1H) MS: MS *m/z* 842.7 (M^++1).

Preparation of Compound 5291 and Compound 5292



Compound 5291



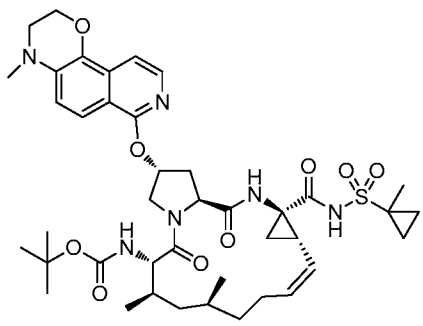
Compound 5292

Compounds 5291 and 5292 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

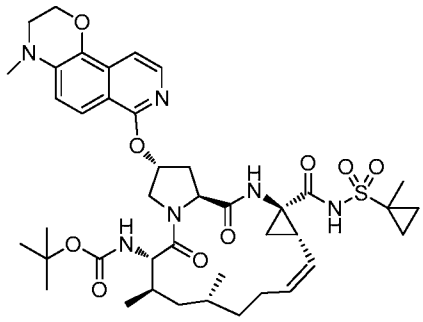
Compound 5291: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 819.6 (M^++1).

Compound 5292: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (br. s., 1H), 8.96 (br. s., 1H), 7.81 (d, *J*=6.1 Hz, 1H), 7.59 (d, *J*=9.2 Hz, 1H), 7.37 (m, 1H), 7.26 (d, *J*=6.1 Hz, 1H), 7.12 (d, *J*=9.2 Hz, 1H), 5.79 (br. s., 1H), 5.50 (m, 1H), 5.08 (m, 1H), 4.68 (t, *J*=6.9 Hz, 1H), 4.48 - 4.32 (m, 4H), 3.97 - 3.86 (m, 2H), 3.77 (t, *J*=9.8 Hz, 1H), 3.41 (m, 2H), 2.99 (s, 3H), 2.95-2.28 (m, 3H), 2.34 - 2.22 (m, 2H), 2.03 - 1.89 (m, 2H), 1.89 - 1.77 (m, 2H), 1.59-1.14 (m, 13H), 0.94-0.85 (m, 6H), 0.72 (m, 1H), 0.42 - 0.28 (m, 2H); MS: MS *m/z* 819.6 (M^++1).

Preparation of Compound 5293 and Compound 5294



Compound 5293



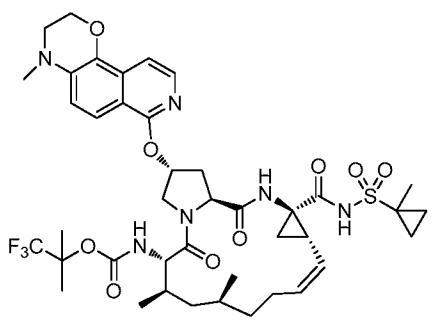
Compound 5294

Compounds 5293 and 5294 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

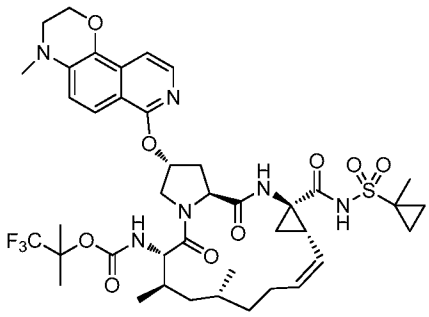
Compound 5293: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 809.5 (M^++1).

Compound 5294: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.09 (br. s., 1H), 7.81 (d, *J*=6.1 Hz, 1H), 7.62 (d, *J*=9.2 Hz, 1H), 7.24 (d, *J*=6.1 Hz, 1H), 7.17 (br. s., 1H), 7.06 (d, *J*=9.2 Hz, 1H), 5.79 (br. s., 1H), 5.52 (m, 1H), 4.97 (m, 1H), 4.52-4.37 (m, 4H), 3.97 - 3.85 (m, 1H), 3.73 (t, *J*=9.5 Hz, 1H), 3.40 (m, 2H), 2.98 (s, 3H), 2.95-2.28 (m, 3H), 2.41 - 2.24 (m, 2H), 1.92 - 1.09 (m, 23H), 0.97 - 0.85 (m, 6H), 0.73 (m, 1H); MS: MS *m/z* 809.5 (M^++1).

Preparation of Compound 5295 and Compound 5296



Compound 5295



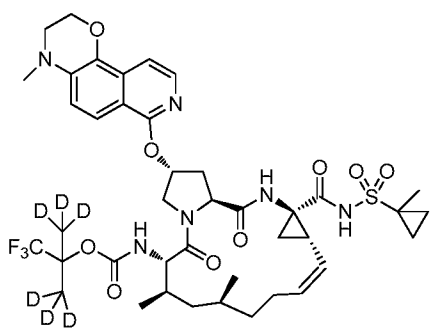
Compound 5296

Compounds 5295 and 5296 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

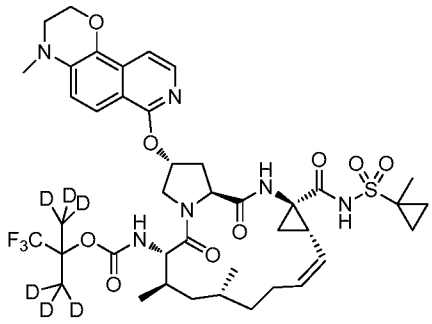
Compound 5295: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 863.5 (M^++1).

Compound 5296: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.14 (br. s., 1H), 7.82 (m, 2H), 7.59 (d, *J*=8.9 Hz, 1H), 7.25 (d, *J*=5.8 Hz, 1H), 7.09 (d, *J*=9.2 Hz, 1H), 5.81 (br. s., 1H), 5.53 (m, 1H), 4.98 (m, 1H), 4.50-4.34 (m, 4H), 3.92 - 3.84 (m, 1H), 3.70 (t, 1H), 3.52 - 3.38 (m, 2H), 2.98 (s, 3H), 2.95-2.28 (m, 3H), 2.38 - 2.23 (m, 2H), 1.94 - 1.24 (m, 17H), 1.10 (s, 3H), 0.95 - 0.86 (m, 6H), 0.74 (br. s., 1H); MS: MS *m/z* 863.5(M^++1).

Preparation of Compound 5297 and Compound 5298



Compound 5297



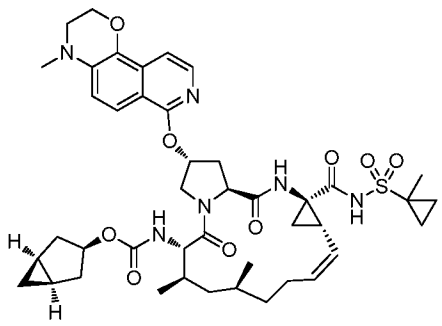
Compound 5298

Compounds 5297 and 5298 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

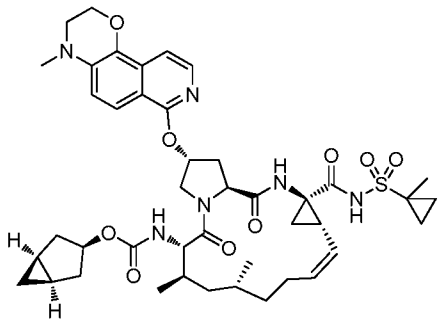
Compound 5297: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 869.7 (M^++1).

Compound 5298: MS: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.15 (br. s., 1H), 7.82 (d, *J*=6.1 Hz, 2H), 7.68 - 7.53 (m, *J*=9.2 Hz, 1H), 7.25 (d, *J*=5.8 Hz, 1H), 7.13 - 7.04 (m, 1H), 5.80 (br. s., 1H), 5.53 (m, 1H), 4.98 (m, 1H), 4.50 (m, 2H), 4.44 - 4.30 (m, 2H), 3.99 - 3.85 (m, 1H), 3.70 (dd, *J*=10.5, 8.4 Hz, 1H), 3.43 (m, 1H), 2.98 (s, 3H), 2.95-2.28 (m, 3H), 2.35 - 2.18 (m, 2H), 2.01 – 1.25 (m, 15H), 0.99 - 0.81 (m, 6H), 0.74 (m, 1H); MS *m/z* 869.7 (M^++1).

Preparation of Compound 5299 and Compound 5300



Compound 5299



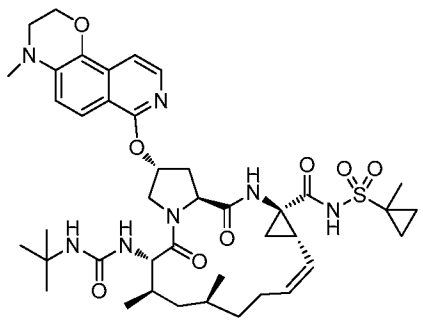
Compound 5300

Compounds 5299 and 5300 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

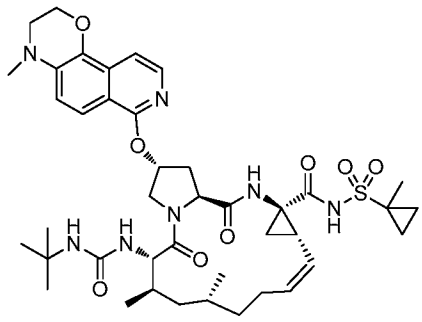
Compound 5299: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 833.6 (M^++1).

Compound 5300: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.15 (br. s., 1H), 7.81 (d, *J*=6.1 Hz, 1H), 7.59 (d, *J*=8.9 Hz, 1H), 7.38 (d, *J*=8.5 Hz, 1H), 7.26 (d, *J*=6.1 Hz, 1H), 7.12 (d, *J*=9.2 Hz, 1H), 5.80 (br. s., 1H), 5.49 (m, 1H), 5.01 (m, 1H), 4.66 (t, *J*=6.9 Hz, 1H), 4.48 - 4.28 (m, 4H), 3.98 - 3.86 (m, 1H), 3.81 - 3.69 (m, 1H), 3.48 - 3.39 (m, 2H), 2.99 (s, 3H), 2.95-2.28 (m, 3H), 2.34 - 2.23 (m, 2H), 2.03 - 1.13 (m, 20H), 0.92 (d, *J*=7.0 Hz, 3H), 0.86 (d, *J*=6.4 Hz, 3H), 0.73 (m, 1H), 0.41 - 0.25 (m, 2H); MS: MS *m/z* 833.6 (M^++1).

Preparation of Compound 5301 and Compound 5302



Compound 5301



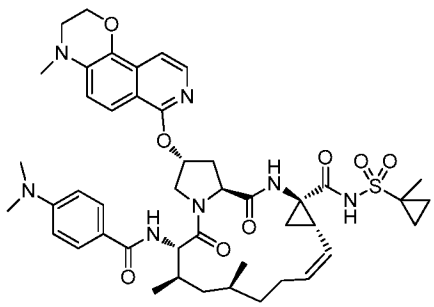
Compound 5302

Compounds 5301 and 5302 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

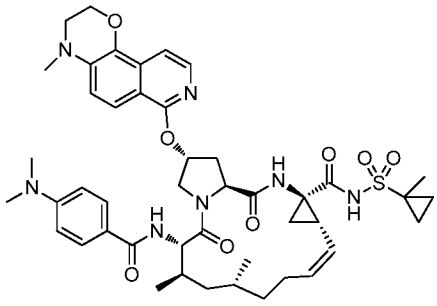
Compound 5301: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide; MS: MS *m/z* 808.6 (M^++1).

Compound 5302: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.07 (br. s., 1H), 7.81 (d, *J*=6.1 Hz, 1H), 7.63 (d, *J*=9.2 Hz, 1H), 7.25 (d, *J*=6.1 Hz, 1H), 7.04 (d, *J*=9.2 Hz, 1H), 5.97 (d, *J*=8.9 Hz, 1H), 5.80 (br. s., 1H), 5.59 (s, 1H), 5.52 (d, *J*=5.2 Hz, 1H), 4.98 (t, *J*=9.9 Hz, 1H), 4.51 (d, *J*=11.3 Hz, 1H), 4.46 - 4.28 (m, 3H), 3.99 - 3.75 (m, 2H), 3.41 (d, *J*=4.0 Hz, 2H), 2.98 (s, 3H), 2.77 - 2.66 (m, 1H), 2.56 (m, 2H), 2.36 (m, 1H), 2.32 - 2.20 (m, 1H), 2.00 - 1.85 (m, 1H), 1.79 - 1.07 (m, 12H), 1.08 (s, 9H), 0.92 (m, 7H), 0.74 (m, 1H); MS: MS *m/z* 808.6 (M^++1).

Preparation of Compound 5303 and Compound 5304



Compound 5303



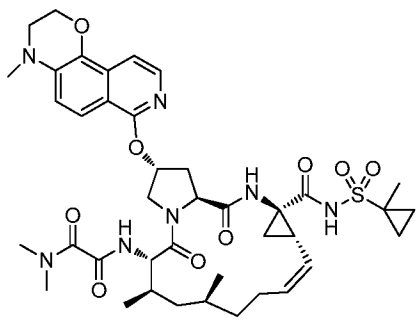
Compound 5304

Compounds 5303 and 5304 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

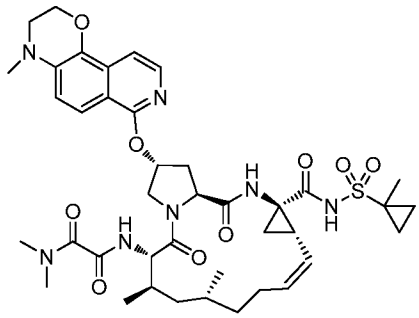
Compound 5303: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(4-(dimethylamino)benzamido)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 856.6 (M^++1).

Compound 5304: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(4-(dimethylamino)benzamido)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.73 (d, *J*=6.4 Hz, 1H), 7.60 - 7.48 (m, 3H), 7.38 (d, *J*=6.4 Hz, 1H), 6.80 (d, *J*=9.2 Hz, 1H), 6.67 (d, *J*=8.9 Hz, 2H), 5.83 (br. s., 1H), 5.59 (m, 1H), 5.00 (t, *J*=9.9 Hz, 1H), 4.58 (dd, *J*=9.6, 7.5 Hz, 1H), 4.48 (d, *J*=11.0 Hz, 1H), 4.39 (m, 2H), 4.09 (dd, *J*=11.6, 3.4 Hz, 1H), 3.43 (t, *J*=4.1 Hz, 2H), 3.04 - 2.92 (m, 10H), 2.79 - 2.69 (m, 2H), 2.47 - 2.31 (m, 2H), 2.19 - 2.08 (m, 1H), 2.05 - 1.94 (m, 1H), 1.86 - 1.70 (m, 2H), 1.69 - 1.60 (m, 1H), 1.56 - 1.38 (m, 8H), 1.28 - 1.17 (m, 1H), 1.01 (d, *J*=6.7 Hz, 6H), 0.93 - 0.84 (m, 2H); MS: MS *m/z* 856.6 (M^++1).

Preparation of Compound 5305 and Compound 5306



Compound 5305



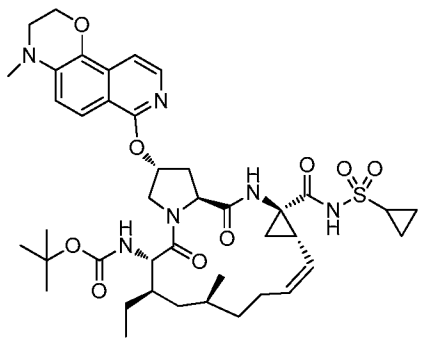
Compound 5306

Compounds 5305 and 5306 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

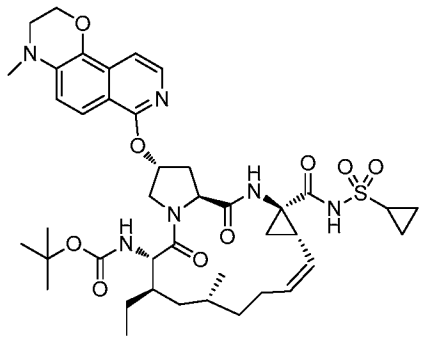
Compound 5305: N1-((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-N2,N2-dimethyloxalamide. MS: MS *m/z* 808.6 (M^++1).

Compound 5306: N1-((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-N2,N2-dimethyloxalamide. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.00 (br. s., 1H), 9.10 (br. s., 1H), 8.99 (d, *J*=8.2 Hz, 1H), 7.81 (d, *J*=6.1 Hz, 1H), 7.54 (d, *J*=8.9 Hz, 1H), 7.26 (d, *J*=6.1 Hz, 1H), 7.15 (d, *J*=9.2 Hz, 1H), 5.83 (br. s., 1H), 5.52 (m, 1H), 5.01 (m, 1H), 4.52 - 4.29 (m, 4H), 4.20 - 4.09 (m, 1H), 4.04 (dd, *J*=11.3, 3.4 Hz, 1H), 3.92 (s, 1H), 3.45 - 3.40 (m, 2H), 3.00 (s, 3H), 2.78 (s, 3H), 2.75-2.55 (m, 2H), 2.67 (s, 3H), 2.32 (m, 2H), 1.92 (m, 2H), 1.75-1.17 (m, 12 H), 0.92 (dd, *J*=17.7, 6.7 Hz, 6H), 0.80 (m, 1H); MS: MS *m/z* 808.6 (M^++1).

Preparation of Compound 5307 and Compound 5308



Compound 5307



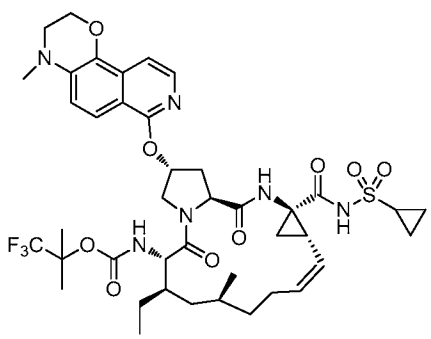
Compound 5308

Compounds 5307 and 5308 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

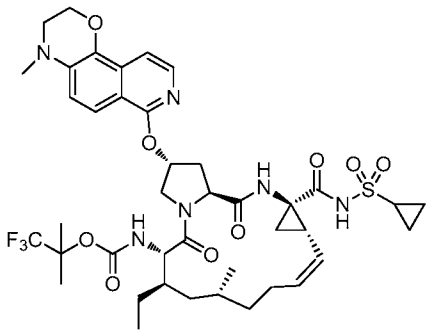
Compound 5307: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 809.5 (M^++1).

Compound 5308: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.97 (br. s., 1H), 7.82 (d, *J*=6.1 Hz, 1H), 7.60 (d, *J*=9.2 Hz, 1H), 7.25 (d, *J*=6.4 Hz, 1H), 7.18 (d, *J*=8.5 Hz, 1H), 7.06 (d, *J*=9.2 Hz, 1H), 5.79 (br. s., 1H), 5.53 (d, *J*=4.9 Hz, 1H), 5.10 - 4.98 (m, 1H), 4.55 (d, *J*=11.6 Hz, 1H), 4.45 - 4.34 (m, 3H), 4.01 - 3.84 (m, 2H), 3.40 (d, *J*=2.4 Hz, 2H), 2.98 (s, 3H), 2.95 - 2.88 (m, 1H), 2.75 - 2.63 (m, 1H), 2.63 - 2.55 (m, 1H), 2.36 - 2.22 (m, 2H), 1.92 (m, 2H), 1.60-1.38 (m, 7H), 1.18 (s, 9H), 1.06-0.93 (m, 9H), 0.74 (m, 3H); MS *m/z* 809.5 (M^++1).

Preparation of Compound 5309 and Compound 5310



Compound 5309



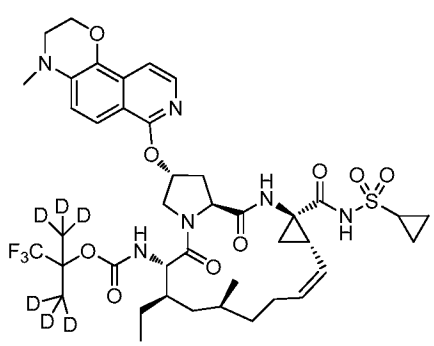
Compound 5310

Compounds 5309 and 5310 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

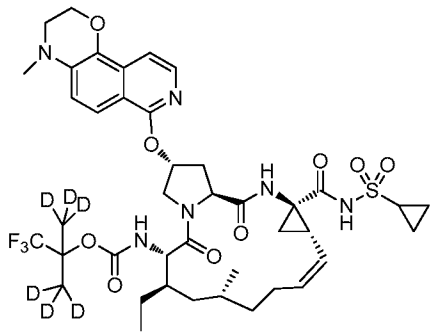
Compound 5309: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 863.5 (M^++1).

Compound 5310: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.97 (br. s., 1H), 7.83 (d, *J*=6.1 Hz, 2H), 7.58 (d, *J*=9.2 Hz, 1H), 7.25 (d, *J*=6.1 Hz, 1H), 7.09 (d, *J*=9.2 Hz, 1H), 5.81 (br. s., 1H), 5.52 (br. s., 1H), 5.07 (br. s., 1H), 4.48 (d, *J*=9.8 Hz, 2H), 4.43 - 4.30 (m, 2H), 3.98 - 3.83 (m, 2H), 3.46 - 3.38 (m, 1H), 2.98 (s, 3H), 2.90 (s, 1H), 2.65-2.59 (m, 2H), 2.36 - 2.20 (m, 2H), 2.03 - 1.88 (m, 2H), 1.69 – 0.92 (m, 23H), 0.73 (m, 3H); MS *m/z* 863.5 (M^++1).

Preparation of Compound 5311 and Compound 5312



Compound 5311



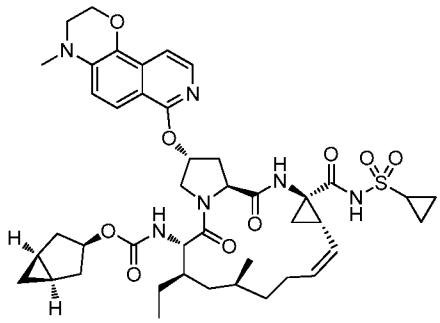
Compound 5312

Compounds 5311 and 5312 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

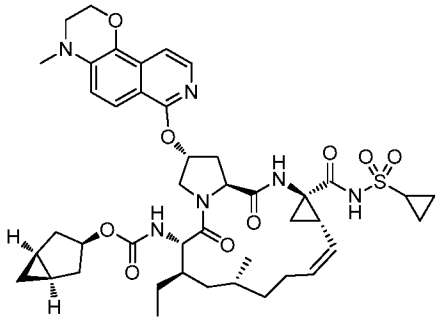
Compound 5311: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 869.6 (M^++1).

Compound 5312: 1,1,1,3,3,3-hexadeutero-2-(trifluoromethyl)propan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (s, 1H), 9.01 (br. s., 1H), 7.83 (d, *J*=5.8 Hz, 2H), 7.57 (d, *J*=8.9 Hz, 1H), 7.25 (d, *J*=6.1 Hz, 1H), 7.09 (d, *J*=8.9 Hz, 1H), 5.81 (br. s., 1H), 5.53 (d, *J*=6.4 Hz, 1H), 5.06 (t, *J*=9.8 Hz, 1H), 4.55 - 4.42 (m, 2H), 4.42 - 4.30 (m, 2H), 3.94 - 3.84 (m, 2H), 3.46 - 3.37 (m, 2H), 2.98 (s, 3H), 2.93 - 2.86 (m, 1H), 2.72 - 2.57 (m, 2H), 2.35 - 2.23 (m, 2H), 2.01 - 1.85 (m, 2H), 1.60 (d, *J*=6.7 Hz, 1H), 1.55 (m, 1H), 1.52 - 1.29 (m, 5H), 1.25 - 1.05 (m, 3H), 1.05 - 0.88 (m, 6H), 0.73 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 869.6 (M^++1).

Preparation of Compound 5313 and Compound 5314



Compound 5313



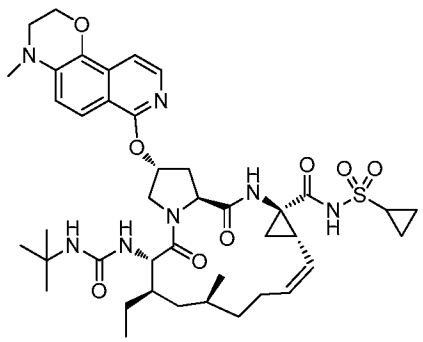
Compound 5314

Compounds 5313 and 5314 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

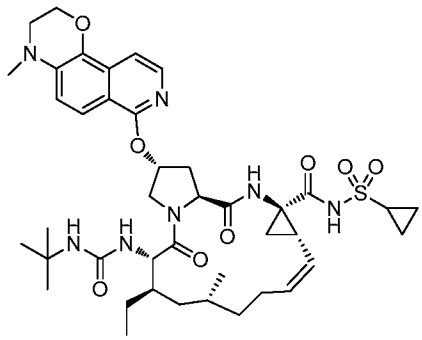
Compound 5313: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 833.5 (M^++1).

Compound 5314: (1R,3r,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (br. s., 1H), 8.95 (br. s., 1H), 7.82 (d, *J*=6.1 Hz, 1H), 7.58 (d, *J*=8.9 Hz, 1H), 7.39 (d, *J*=9.2 Hz, 1H), 7.26 (d, *J*=6.1 Hz, 1H), 7.12 (d, *J*=9.2 Hz, 1H), 5.80 (br. s., 1H), 5.51 (br. s., 1H), 5.08 (br. s., 1H), 4.66 (t, *J*=6.7 Hz, 1H), 4.51 - 4.31 (m, 4H), 4.06 - 3.83 (m, 2H), 3.46 - 3.38 (m, 2H), 2.99 (s, 3H), 2.90 (m, 1H), 2.75-2.57 (m, 2H), 2.29 (m, 2H), 2.03 - 1.87 (m, 3H), 1.82 - 1.74 (m, 1H), 1.58-0.92 (m, 20H), 0.73 (t, *J*=7.5 Hz, 3H), 0.42 - 0.31 (m, 2H); MS: MS *m/z* 833.5 (M^++1).

Preparation of Compound 5315 and Compound 5316



Compound 5315



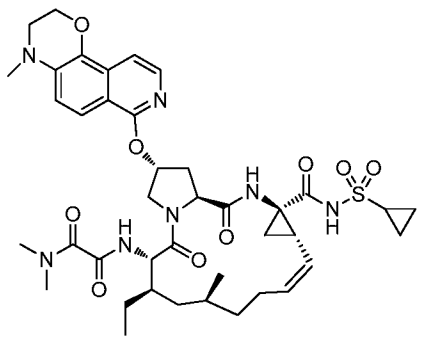
Compound 5316

Compounds 5315 and 5316 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

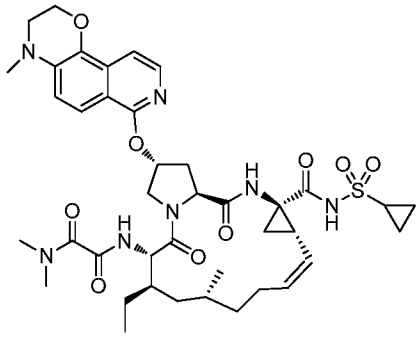
Compound 5315: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-N-(cyclopropylsulfonyl)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 808.5 (M^++1).

Compound 5316: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(3-(tert-butyl)ureido)-N-(cyclopropylsulfonyl)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.17 (br. s., 1H), 8.91 (br. s., 1H), 7.81 (d, *J*=6.1 Hz, 1H), 7.62 (d, *J*=9.2 Hz, 1H), 7.25 (d, *J*=6.4 Hz, 1H), 7.04 (d, *J*=9.2 Hz, 1H), 5.95 (d, *J*=9.5 Hz, 1H), 5.79 (br. s., 1H), 5.60 (s, 1H), 5.49 (br. s., 1H), 5.09 (br. s., 1H), 4.52 (d, *J*=9.5 Hz, 1H), 4.45 - 4.30 (m, 3H), 4.09 (t, *J*=10.2 Hz, 1H), 3.96 - 3.84 (m, 1H), 3.43 - 3.38 (m, 2H), 2.98 (s, 3H), 2.92 - 2.84 (m, 1H), 2.56 (m, 2H), 2.35 - 2.19 (m, 2H), 1.96 - 1.84 (m, 1H), 1.78 - 1.70 (m, 1H), 1.57-0.92 (m, 25H), 0.79 (t, *J*=7.3 Hz, 3H); MS: MS *m/z* 808.5 (M^++1).

Preparation of Compound 5317 and Compound 5318



Compound 5317



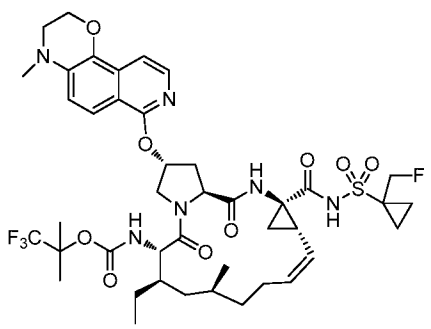
Compound 5318

Compounds 5317 and 5318 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

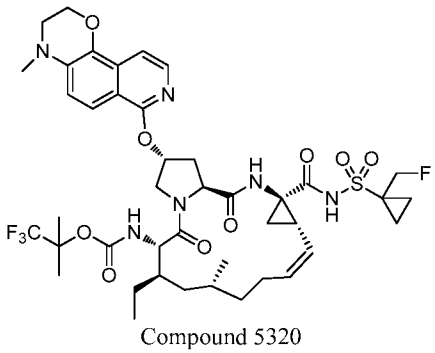
Compound 5317: N1-((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-N2,N2-dimethyloxalamide MS: MS *m/z* 808.5 (M^++1).

Compound 5318: N1-((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-N2,N2-dimethyloxalamide ^{1}H NMR (500MHz, DMSO-d_6) δ 11.15 (br. s., 1H), 9.08 - 8.88 (m, 2H), 7.82 (d, *J*=6.1 Hz, 1H), 7.53 (d, *J*=8.9 Hz, 1H), 7.26 (d, *J*=6.1 Hz, 1H), 7.15 (d, *J*=9.2 Hz, 1H), 5.83 (br. s., 1H), 5.60 - 5.45 (m, 1H), 5.09 (t, *J*=9.8 Hz, 1H), 4.51 - 4.28 (m, 5H), 4.02 (dd, *J*=11.4, 3.8 Hz, 1H), 3.42 (dd, *J*=5.0, 3.2 Hz, 2H), 3.00 (s, 3H), 2.91 (d, *J*=4.9 Hz, 1H), 2.79 (s, 3H), 2.70 (s, 3H), 2.61 (dd, *J*=13.6, 6.9 Hz, 1H), 2.39 - 2.24 (m, 2H), 2.06 (t, *J*=10.5 Hz, 1H), 2.00 - 1.86 (m, 1H), 1.65 - 1.38 (m, 7H), 1.18-0.94 (m, 10H), 0.76 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 808.5 (M^++1).

Preparation of Compound 5319 and Compound 5320



Compound 5319



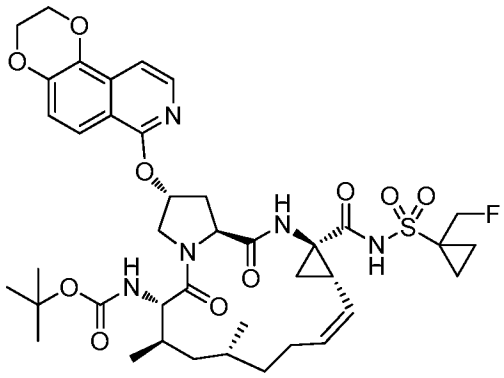
Compound 5320

Compounds 5319 and 5320 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5319: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 881.6 (M^++1).

Compound 5320: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.06 (br. s., 1H), 7.82 (d, *J*=6.1 Hz, 2H), 7.59 (d, *J*=8.9 Hz, 1H), 7.25 (d, *J*=6.1 Hz, 1H), 7.08 (d, *J*=9.2 Hz, 1H), 5.79 (br. s., 1H), 5.51 (m, 1H), 4.99 (t, *J*=10.1 Hz, 1H), 4.87-4.58 (m, 2H), 4.49 (d, *J*=11.6 Hz, 2H), 4.44 - 4.31 (m, 2H), 3.94 - 3.85 (m, 1H), 3.71 (dd, *J*=10.5, 8.4 Hz, 1H), 3.40 (m, 2H), 2.98 (s, 3H), 2.72 - 2.62 (m, 2H), 2.36 - 2.23 (m, 2H), 1.85 (m, 2H), 1.69 (m, 1H), 1.53 (m, 4H), 1.39 (m, 5H), 1.25 (m, 3H), 1.15 (s, 3H), 0.98 - 0.84 (m, 6H), 0.80 - 0.70 (m, 1H); MS: MS *m/z* 881.6 (M^++1).

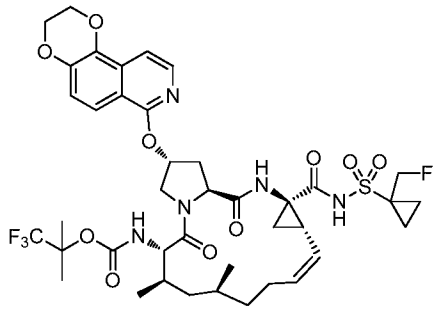
Preparation of Compound 5321



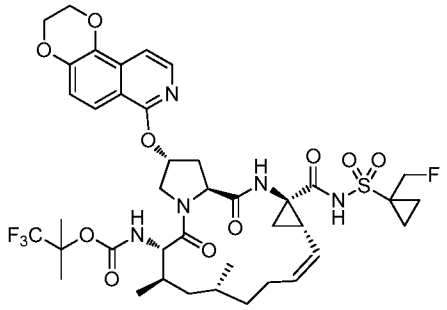
Compound 5321

Compound 5321 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117: Compound 5321: MS: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.03 (s, 1H), 7.97 (d, *J*=6.1 Hz, 1H), 7.66 (d, *J*=8.9 Hz, 1H), 7.38 (d, *J*=6.1 Hz, 1H), 7.18 (d, *J*=8.2 Hz, 1H), 7.08 (d, *J*=8.9 Hz, 1H), 5.80 (br. s., 1H), 5.59 - 5.44 (m, 1H), 5.01 - 4.75 (m, 2H), 4.59 (d, *J*=8.2 Hz, 1H), 4.52 - 4.31 (m, 6H), 3.98 - 3.83 (m, 2H), 3.71 (dd, *J*=10.7, 8.2 Hz, 1H), 2.71 - 2.56 (m, 2H), 2.37 - 2.24 (m, 2H), 1.92-1.67 (m, 2H), 1.59 - 1.08 (m, 18H), 0.96 - 0.81 (m, 6H), 0.73 (t, *J*=12.5 Hz, 1H); MS *m/z* 814.4 (M^++1).

Preparation of Compound 5322 and Compound 5323



Compound 5322



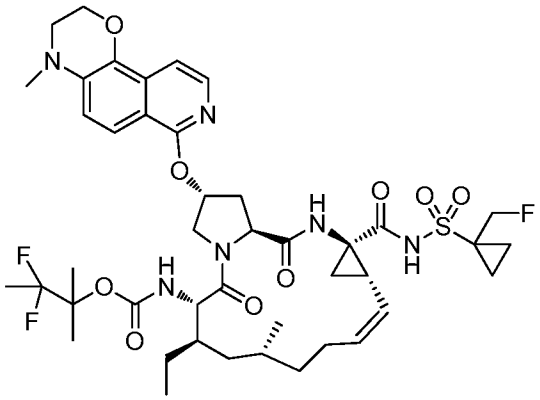
Compound 5323

Compounds 5322 and 5323 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5322: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 868.4 (M^++1).

Compound 5323: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.06 (s, 1H), 7.98 (d, *J*=6.1 Hz, 2H), 7.63 (d, *J*=8.9 Hz, 1H), 7.38 (d, *J*=6.1 Hz, 1H), 7.13 (d, *J*=8.9 Hz, 1H), 5.81 (br. s., 1H), 5.59 - 5.40 (m, 1H), 4.99 (t, *J*=10.1 Hz, 1H), 4.86-4.76 (m, 1H), 4.64 - 4.30 (m, 7H), 3.94 - 3.87 (m, 1H), 3.70 (dd, *J*=10.7, 8.2 Hz, 1H), 2.69 - 2.56 (m, 2H), 2.38 - 2.25 (m, 2H), 1.96 - 1.77 (m, 2H), 1.74 - 1.64 (m, 1H), 1.53 (m, 4H), 1.46 - 1.31 (m, 6H), 1.30 - 1.19 (m, 2H), 1.12 (s, 3H), 0.98 - 0.87 (m, 6H), 0.75 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 868.4 (M^++1).

Preparation of Compound 5324

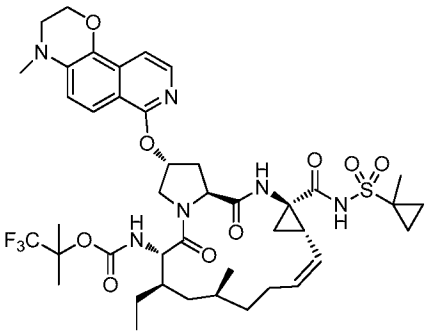


Compound 5324

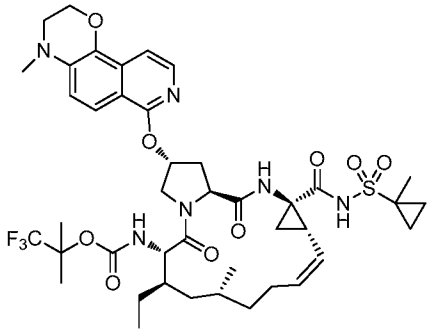
Compound 5324 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5324: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (br. s., 1H), 9.04 (br. s., 1H), 7.82 (d, *J*=6.1 Hz, 1H), 7.60 (d, *J*=9.2 Hz, 2H), 7.25 (d, *J*=5.8 Hz, 1H), 7.07 (d, *J*=9.2 Hz, 1H), 5.80 (br. s., 1H), 5.51 (br. s., 1H), 5.00 (t, *J*=9.6 Hz, 1H), 4.87-4.60 (m, 2H), 4.48 - 4.36 (m, 5H), 3.95 - 3.86 (m, 1H), 3.73 (dd, *J*=10.7, 8.5 Hz, 1H), 3.40 (m, 1H), 2.98 (s, 3H), 2.69-2.59(m, 2H), 2.37 - 2.21 (m, 2H), 1.97 - 1.16 (m, 18H), 1.08 (s, 3H), 0.98 - 0.87 (m, 6H), 0.75 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 877.4 (M^++1).

Preparation of Compound 5325 and Compound 5326



Compound 5325



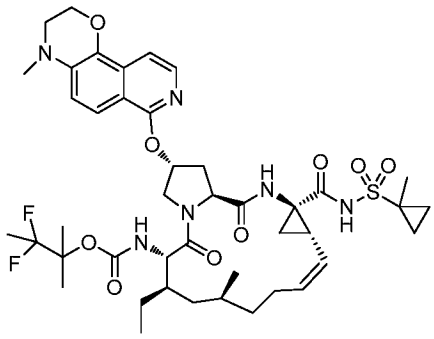
Compound 5326

Compounds 5325 and 5326 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

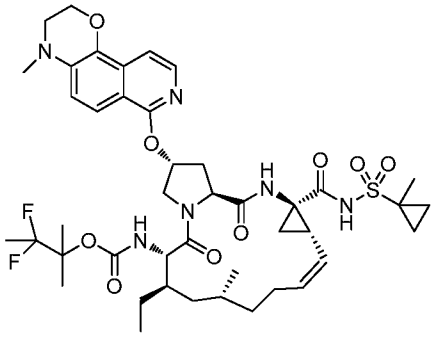
Compound 5325: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 877.5 (M^++1).

Compound 5326: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.14 (br. s., 1H), 7.93 - 7.77 (m, 2H), 7.57 (d, *J*=9.2 Hz, 1H), 7.25 (d, *J*=6.1 Hz, 1H), 7.09 (d, *J*=8.9 Hz, 1H), 5.82 (br. s., 1H), 5.53 (d, *J*=4.9 Hz, 1H), 4.98 (m, 1H), 4.58 - 4.43 (m, 2H), 4.43 - 4.23 (m, 2H), 3.99 - 3.80 (m, 2H), 3.46 - 3.37 (m, 2H), 2.98 (s, 3H), 2.75 - 2.65 (m, 1H), 2.60 (d, *J*=7.0 Hz, 1H), 2.40 - 2.24 (m, 2H), 2.04 - 1.86 (m, 2H), 1.62 (m, 1H), 1.56 – 0.82 (m, 24H), 0.73 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 877.5 (M^++1).

Preparation of Compound 5327 and Compound 5328



Compound 5327



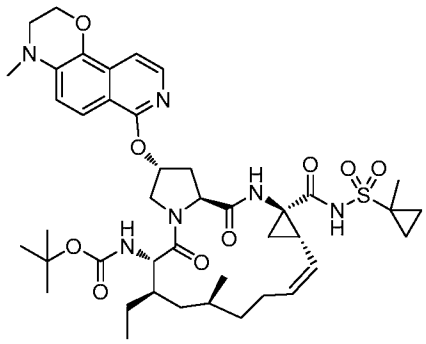
Compound 5328

Compounds 5327 and 5328 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

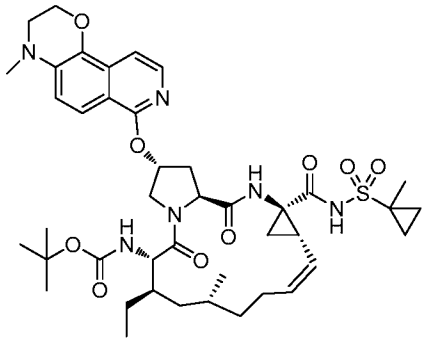
Compound 5327: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 873.5 (M^++1).

Compound 5328: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.11 (br. s., 1H), 7.82 (d, *J*=6.1 Hz, 1H), 7.69 - 7.51 (m, 2H), 7.25 (d, *J*=6.1 Hz, 1H), 7.08 (d, *J*=9.2 Hz, 1H), 5.82 (br. s., 1H), 5.52 (m, 1H), 4.99 (m, 1H), 4.59 - 4.43 (m, 2H), 4.43 - 4.23 (m, 2H), 4.04 - 3.85 (m, 2H), 3.47 - 3.37 (m, 2H), 2.98 (s, 3H), 2.79 - 2.68 (m, 1H), 2.59 (m, 1H), 2.35 - 2.21 (m, 2H), 2.05 - 1.85 (m, 2H), 1.62-1.16 (m, 19H), 1.01 – 0.92 (m, 9H), 0.74 (s, 3H); MS: MS *m/z* 873.5 (M^++1).

Preparation of Compound 5329 and Compound 5330



Compound 5329



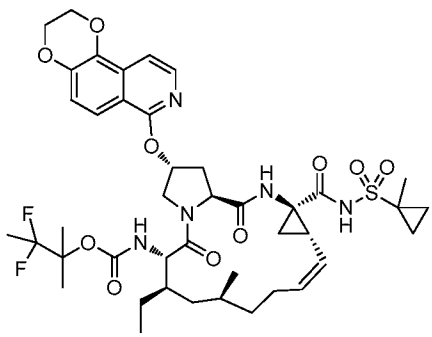
Compound 5330

Compounds 5329 and 5330 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

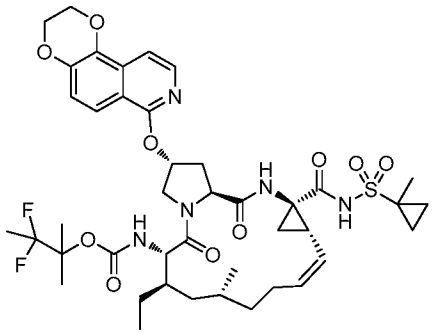
Compound 5329: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 823.5 (M^++1).

Compound 5330: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.09 (br. s., 1H), 7.82 (d, *J*=6.1 Hz, 1H), 7.60 (d, *J*=9.2 Hz, 1H), 7.29 - 7.13 (m, 2H), 7.06 (d, *J*=8.9 Hz, 1H), 5.81 (br. s., 1H), 5.52 (m, 1H), 4.98 (m, 1H), 4.64 - 4.29 (m, 4H), 4.01 - 3.76 (m, 2H), 3.40 (d, *J*=2.7 Hz, 2H), 2.98 (s, 3H), 2.80 - 2.55 (m, 2H), 2.40 - 2.24 (m, 2H), 1.99 - 1.85 (m, 2H), 1.70 - 1.24 (m, 12H), 1.17 (s, 9H), 1.05 (m, 2H), 0.93 (m, 5H), 0.74 (s, 3H); MS: MS *m/z* 823.5 (M^++1).

Preparation of Compound 5331 and Compound 5332



Compound 5331



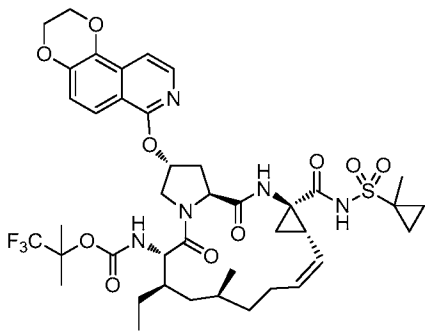
Compound 5332

Compounds 5331 and 5332 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

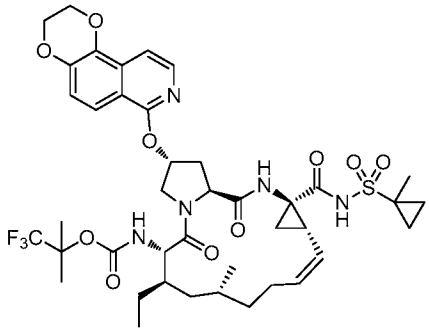
Compound 5331: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 860.8 (M^++1).

Compound 5332: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.11 (s, 1H), 7.98 (d, *J*=5.8 Hz, 1H), 7.73 - 7.55 (m, 2H), 7.39 (d, *J*=6.1 Hz, 1H), 7.12 (d, *J*=8.9 Hz, 1H), 5.84 (br. s., 1H), 5.62 - 5.44 (m, 1H), 4.98 (t, *J*=9.9 Hz, 1H), 4.60 - 4.27 (m, 6H), 3.98 - 3.81 (m, 2H), 2.79 - 2.57 (m, 2H), 2.39 - 2.22 (m, 2H), 1.93 (d, *J*=9.8 Hz, 2H), 1.69 - 1.09 (m, 20H), 1.02 - 0.84 (m, 8H), 0.74 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 860.8 (M^++1).

Preparation of Compound 5333 and Compound 5334



Compound 5333



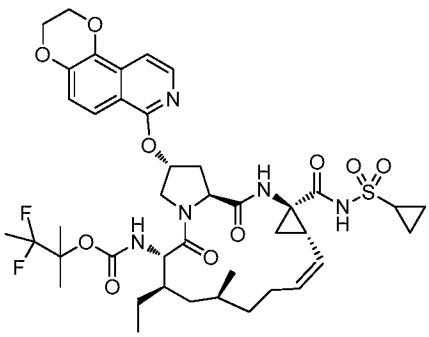
Compound 5334

Compounds 5333 and 5334 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

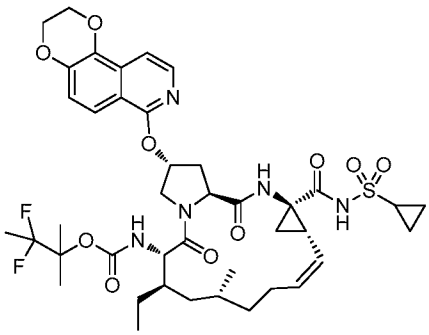
Compound 5333: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 864.4 (M^++1).

Compound 5334: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (s, 1H), 9.14 (s, 1H), 7.98 (d, *J*=5.8 Hz, 1H), 7.86 (d, *J*=8.2 Hz, 1H), 7.61 (d, *J*=8.9 Hz, 1H), 7.39 (d, *J*=5.8 Hz, 1H), 7.13 (d, *J*=8.9 Hz, 1H), 5.84 (br. s., 1H), 5.61 - 5.48 (m, 1H), 4.98 (t, *J*=10.1 Hz, 1H), 4.60 - 4.32 (m, 6H), 4.03 - 3.84 (m, 2H), 2.82 - 2.58 (m, 2H), 2.39 - 2.26 (m, 2H), 2.05 - 1.84 (m, 2H), 1.66 - 0.97 (m, 21H), 0.95 - 0.87 (m, 4H), 0.73 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 864.4 (M^++1).

Preparation of Compound 5335 and Compound 5336



Compound 5335



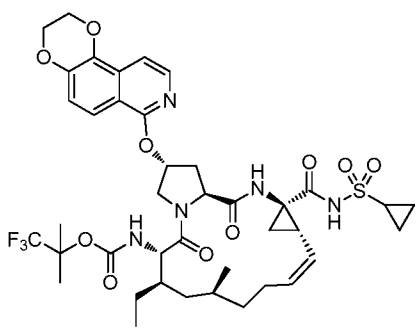
Compound 5336

Compounds 5335 and 5336 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

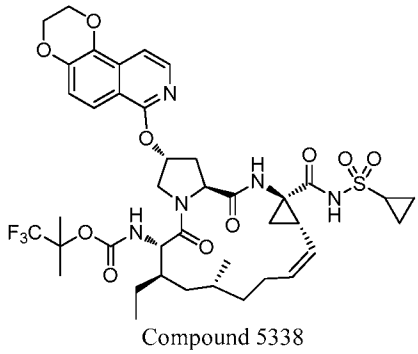
Compound 5335: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 846.5 (M^++1).

Compound 5336: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (s, 1H), 8.99 (s, 1H), 7.98 (d, *J*=5.8 Hz, 1H), 7.70 - 7.55 (m, 2H), 7.39 (d, *J*=6.1 Hz, 1H), 7.12 (d, *J*=9.2 Hz, 1H), 5.82 (br. s., 1H), 5.62 - 5.45 (m, 1H), 5.06 (t, *J*=9.6 Hz, 1H), 4.62 - 4.29 (m, 6H), 4.02 - 3.81 (m, 2H), 2.96 - 2.88 (m, 1H), 2.75 - 2.59 (m, 2H), 2.36 - 2.22 (m, 2H), 1.93 (d, *J*=6.4 Hz, 2H), 1.66 - 1.33 (m, 10H), 1.28 (s, 3H), 1.24 - 0.88 (m, 12H), 0.74 (t, *J*=7.3 Hz, 3H); MS: MS *m/z* 846.5 (M^++1).

Preparation of Compound 5337 and Compound 5338



Compound 5337



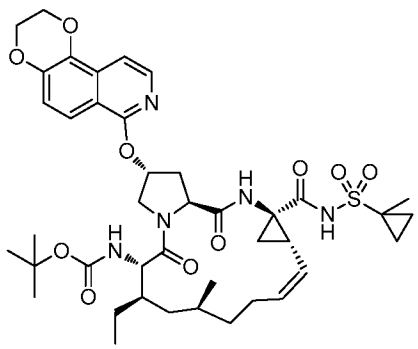
Compound 5338

Compounds 5337 and 5338 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

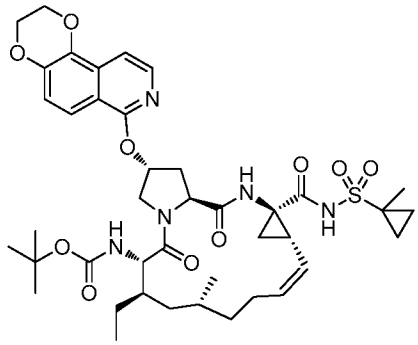
Compound 5337: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 850.7 (M^++1).

Compound 5338: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.01 (s, 1H), 8.06 - 7.76 (m, 2H), 7.61 (d, *J*=8.9 Hz, 1H), 7.39 (d, *J*=5.8 Hz, 1H), 7.13 (d, *J*=8.9 Hz, 1H), 5.82 (br. s., 1H), 5.61 - 5.45 (m, 1H), 5.05 (t, *J*=9.9 Hz, 1H), 4.61 - 4.29 (m, 6H), 3.97 - 3.77 (m, 2H), 3.00 - 2.86 (m, 1H), 2.80 - 2.57 (m, 2H), 2.31 (ddd, *J*=13.9, 10.2, 4.0 Hz, 2H), 2.04 - 1.89 (m, 2H), 1.69 - 1.27 (m, 10H), 1.20 - 0.85 (m, 12H), 0.73 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 850.7 (M^++1).

Preparation of Compound 5339 and Compound 5340



Compound 5339



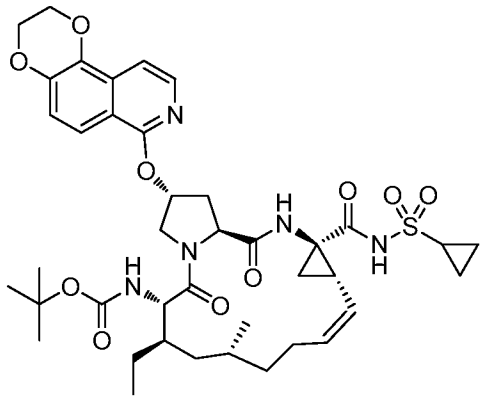
Compound 5340

Compounds 5339 and 5340 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5339: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 810.5 (M^++1).

Compound 5340: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.10 (s, 1H), 7.97 (d, *J*=5.8 Hz, 1H), 7.63 (d, *J*=8.9 Hz, 1H), 7.38 (d, *J*=6.1 Hz, 1H), 7.19 (d, *J*=8.9 Hz, 1H), 7.09 (d, *J*=9.2 Hz, 1H), 5.83 (br. s., 1H), 5.59 - 5.46 (m, 1H), 4.97 (t, *J*=9.9 Hz, 1H), 4.61 (d, *J*=11.3 Hz, 1H), 4.52 - 4.29 (m, 6H), 3.92 (t, *J*=5.2 Hz, 2H), 2.81 - 2.56 (m, 2H), 2.42 - 2.21 (m, 2H), 1.93 (t, *J*=5.8 Hz, 2H), 1.68 - 0.83 (m, 27H), 0.73 (s, 3H); MS: MS *m/z* 810.5 (M^++1).

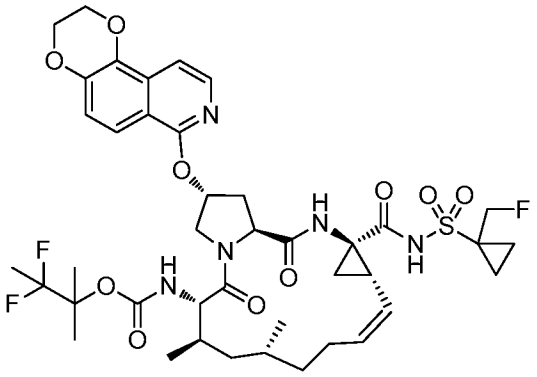
Preparation of Compound 5341



Compound 5341

Compound 5341 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117: Compound 5341: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.97 (br. s., 1H), 7.97 (d, *J*=6.1 Hz, 1H), 7.63 (d, *J*=8.9 Hz, 1H), 7.38 (d, *J*=6.1 Hz, 1H), 7.19 (d, *J*=8.5 Hz, 1H), 7.09 (d, *J*=8.9 Hz, 1H), 5.81 (br. s., 1H), 5.53 (d, *J*=6.7 Hz, 1H), 5.05 (t, *J*=10.1 Hz, 1H), 4.60 (d, *J*=11.6 Hz, 1H), 4.42 (dd, *J*=20.0, 3.8 Hz, 6H), 3.98 - 3.79 (m, 2H), 2.96 - 2.86 (m, 1H), 2.74 - 2.58 (m, 2H), 2.35 - 2.23 (m, 2H), 1.92 (m, 2H), 1.66 - 1.31 (m, 7H), 1.14 (m, 10H), 1.07 - 0.90 (m, 7H), 0.73 (t, *J*=7.5 Hz, 3H); MS: MS m/z 796.5 (M^++1).

Preparation of Compound 5342

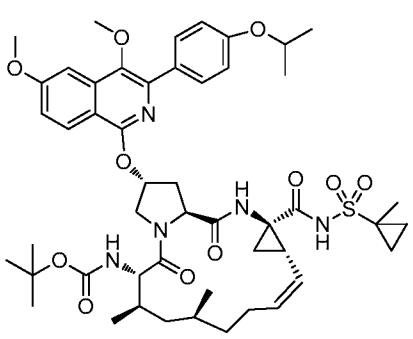


Compound 5342

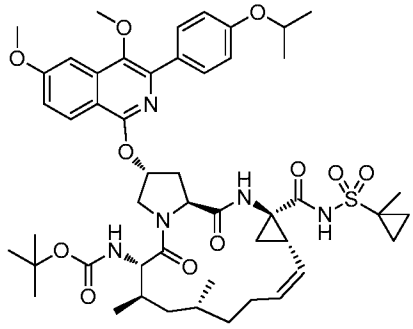
Compound 5342 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5342: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (br. s., 1H), 9.04 (br. s., 1H), 7.98 (d, *J*=5.8 Hz, 1H), 7.68 - 7.54 (m, 2H), 7.38 (d, *J*=5.8 Hz, 1H), 7.11 (d, *J*=8.9 Hz, 1H), 5.81 (br. s., 1H), 5.51 (br. s., 1H), 5.00 (br. s., 1H), 4.90 - 4.57 (m, 2H), 4.55 - 4.27 (m, 6H), 3.96 - 3.84 (m, 1H), 3.71 (dd, *J*=10.4, 8.5 Hz, 1H), 2.73 - 2.56 (m, 2H), 2.39 - 2.26 (m, 2H), 1.98 - 1.11 (m, 18H), 1.04 (s, 3H), 0.96 - 0.86 (m, 6H), 0.75 (t, *J*=12.1 Hz, 1H); MS: MS m/z 864.4 (M^++1).

Preparation of Compound 5343 and Compound 5344



Compound 5343



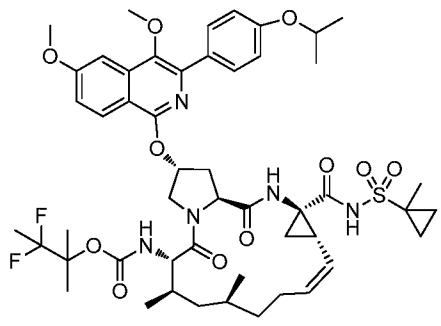
Compound 5344

Compounds 5343 and 5344 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

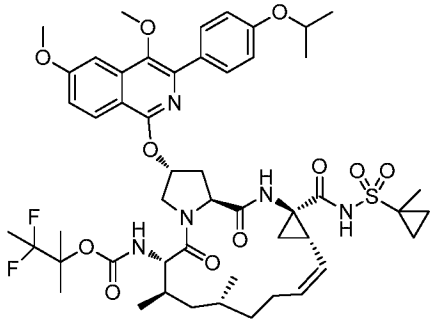
Compound 5343: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(4-isopropoxyphenyl)-4,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 932.6 (M^++1).

Compound 5344: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(4-isopropoxyphenyl)-4,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.08 (br. s., 1H), 9.08 (br. s., 1H), 8.11 (d, *J*=8.5 Hz, 2H), 8.04 (d, *J*=9.2 Hz, 1H), 7.34 (d, *J*=2.4 Hz, 1H), 7.20 (d, *J*=7.9 Hz, 1H), 7.13 (dd, *J*=9.0, 2.3 Hz, 1H), 7.06 (d, *J*=8.5 Hz, 2H), 5.86 (br. s., 1H), 5.53 (br. s., 1H), 4.98 (br. s., 1H), 4.73 (dt, *J*=12.1, 5.9 Hz, 1H), 4.66 - 4.45 (m, 2H), 4.00 - 3.87 (m, 4H), 3.81 - 3.70 (m, 1H), 3.62 (s, 3H), 2.77 - 2.61 (m, 2H), 2.41 - 2.25 (m, 2H), 2.00 - 1.08 (m, 28H), 1.00 - 0.83 (m, 8H), 0.74 (m, 1H); MS: MS m/z 932.6 (M^++1).

Preparation of Compound 5345 and Compound 5346



Compound 5345



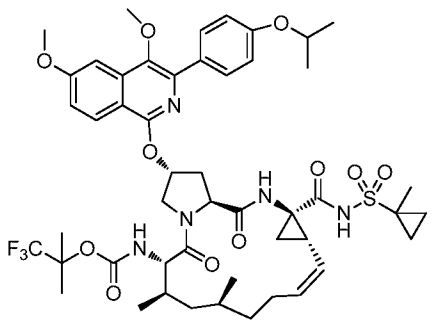
Compound 5346

Compounds 5345 and 5346 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

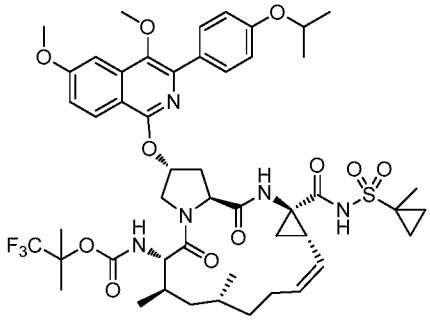
Compound 5345: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(4-isopropoxyphenyl)-4,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 982.6 (M^++1).

Compound 5346: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(4-isopropoxyphenyl)-4,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.07 (s, 1H), 9.09 (br. s., 1H), 8.23 - 7.92 (m, 3H), 7.64 (d, *J*=7.9 Hz, 1H), 7.35 (s, 1H), 7.15 (d, *J*=8.9 Hz, 1H), 7.07 (d, *J*=8.2 Hz, 2H), 5.88 (br. s., 1H), 5.54 (d, *J*=6.1 Hz, 1H), 4.99 (t, *J*=9.6 Hz, 1H), 4.83 - 4.69 (m, 1H), 4.64 - 4.47 (m, 2H), 3.97 (m, 4H), 3.75 (t, *J*=9.6 Hz, 1H), 3.63 (s, 3H), 2.79 - 2.62 (m, 2H), 2.40 - 2.29 (m, 2H), 1.98 - 1.10 (m, 25H), 1.05 (m, 3H), 0.92 (m, 8H), 0.77 (t, *J*=12.2 Hz, 1H); MS: MS m/z 982.6 (M^++1).

Preparation of Compound 5347 and Compound 5348



Compound 5347



Compound 5348

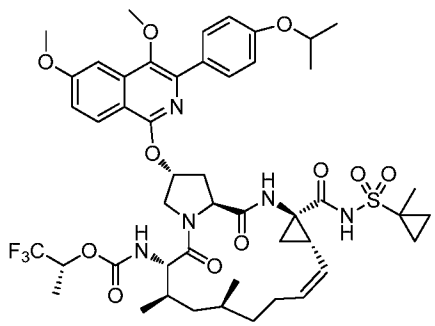
Compounds 5347 and 5348 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5347: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(4-isopropoxyphenyl)-4,6-

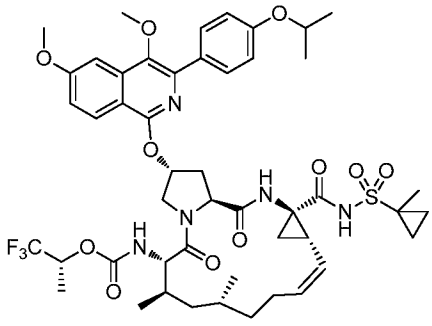
dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 986.5 (M^++1).

Compound 5348: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(4-isopropoxyphenyl)-4,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (br. s., 1H), 9.11 (br. s., 1H), 8.12 (m, 2H), 8.01 (d, *J*=9.2 Hz, 1H), 7.83 (d, *J*=9.8 Hz, 1H), 7.35 (d, *J*=2.4 Hz, 1H), 7.16 (dd, *J*=9.2, 2.4 Hz, 1H), 7.06 (d, *J*=8.9 Hz, 2H), 5.88 (br. s., 1H), 5.53 (br. s., 1H), 4.99 (br. s., 1H), 4.82 - 4.69 (m, 1H), 4.55 (m, 2H), 4.03 - 3.88 (m, 4H), 3.73 (dd, *J*=10.7, 8.2 Hz, 1H), 3.63 (s, 3H), 2.69 (m, 2H), 2.40 - 2.29 (m, 2H), 1.98 - 1.09 (m, 25H), 0.97 - 0.83 (m, 8H), 0.76 (br. s., 1H); MS: MS m/z 986.5 (M^++1).

Preparation of Compound 5349 and Compound 5350



Compound 5349



Compound 5350

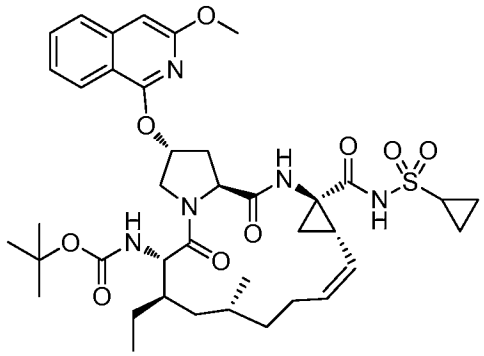
Compounds 5349 and 5350 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5349: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(4-isopropoxyphenyl)-4,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 972.5 (M^++1).

Compound 5350: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(4-isopropoxyphenyl)-4,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.07 (s, 1H), 8.12 (m, 3H), 7.98 (d, *J*=8.9 Hz, 1H), 7.34 (d, *J*=2.4 Hz, 1H), 7.15 - 6.96 (m, 3H), 5.89 (br. s., 1H), 5.53 (d, *J*=5.8 Hz, 1H), 5.00 (t, *J*=9.9 Hz, 1H), 4.81 - 4.65 (m, 2H), 4.60 - 4.40 (m, 2H), 4.03 - 3.92 (m, 4H), 3.80 (dd, *J*=10.7, 8.5 Hz, 1H), 3.64 (s, 3H), 2.69 (d, *J*=9.5 Hz, 2H), 2.39 - 2.25 (m, 2H), 1.91 (d, *J*=13.7 Hz, 2H), 1.68 (d, *J*=11.9 Hz, 1H), 1.60 (d, *J*=4.9 Hz, 1H), 1.53 (br. s., 1H), 1.48 - 1.37 (m, 5H), 1.37 - 1.25 (m, 9H), 1.21 (d, *J*=6.4 Hz, 3H), 0.92 (m, 8H), 0.78 (t, *J*=12.1 Hz, 1H); MS: MS m/z 972.5 (M^++1).

Preparation of Compound 6001



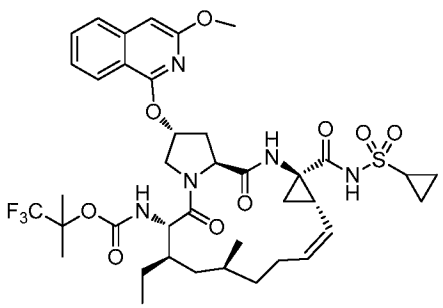
Compound 6001

Compound 6001 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

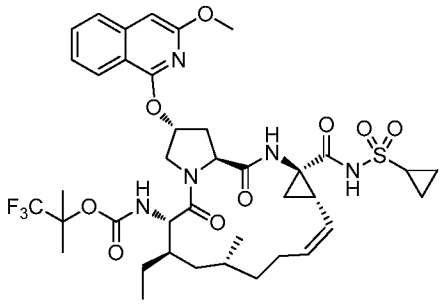
Compound 6001: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, METHANOL-d_4) δ 8.07 (d, *J*=8.5 Hz, 1H), 7.65 (d, *J*=8.2 Hz, 1H), 7.56 (d, *J*=7.9 Hz, 1H), 7.24 (t, *J*=7.5 Hz, 1H), 6.62 (s, 1H), 5.90 (br. s., 1H), 5.53 (td, *J*=10.0, 6.0 Hz, 1H), 5.07 (m, 1H), 4.79 (d, *J*=11.3 Hz, 1H), 4.60 (dd, *J*=9.8,

7.3 Hz, 1H), 4.20 - 4.02 (m, 2H), 4.00 (s, 3H), 2.92 (m, 1H), 2.76 (m, 1H), 2.68 (m, 1H), 2.52 - 2.32 (m, 2H), 1.99 - 1.88 (m, 2H), 1.75 (m, 1H), 1.65 - 1.51 (m, 5H), 1.38 (m, 1H), 1.34 - 1.27 (m, 1H), 1.18 (s, 9H), 1.15 - 1.03 (m, 4H), 1.00 (d, *J*=6.7 Hz, 4H), 0.84 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 768.3 (M^++1).

Preparation of Compound 6002 and Compound 6003



Compound 6002



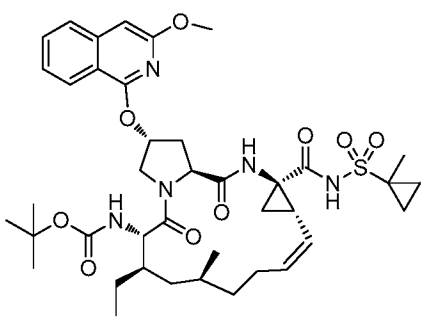
Compound 6003

Compounds 6002 and 6003 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

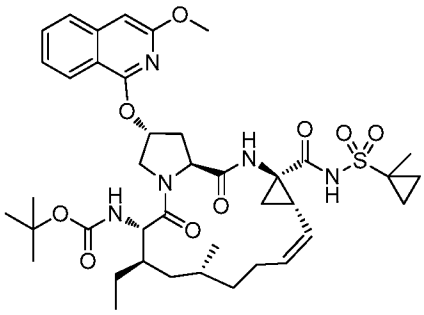
Compound 6002: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 822.3 (M^++1).

Compound 6003: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (br.s, 1H), 9.00 (br.s, 1H), 7.99 (d, *J*=8.5 Hz, 1H), 7.89 (d, *J*=8.5 Hz, 1H), 7.75 (d, *J*=8.2 Hz, 1H), 7.64 (t, *J*=7.6 Hz, 1H), 7.32 (t, *J*=7.6 Hz, 1H), 6.72 (br.s, 1H), 5.81 (br. s., 1H), 5.54 (m, 1H), 5.06 (t, *J*=9.8 Hz, 1H), 4.58 (d, *J*=11.0 Hz, 1H), 4.49 (dd, *J*=9.9, 7.2 Hz, 1H), 3.93 (s, 3H), 3.96-3.90 (m, 2H), 2.92 (m, 1H), 2.77 - 2.61 (m, 2H), 2.42 - 2.25 (m, 2H), 2.02 - 1.85 (m, 2H), 1.66 - 1.43 (m, 7H), 1.39 (s, 3H), 1.26 – 0.93 (m, 9H), 1.10 (s, 3H), 0.74 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 822.3 (M^++1).

Preparation of Compound 6004 and Compound 6005



Compound 6004



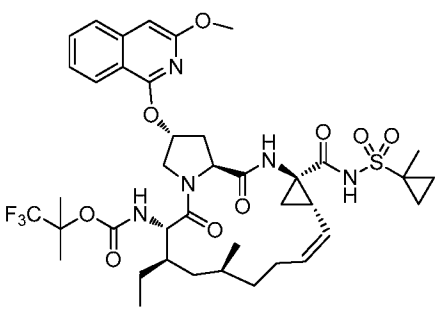
Compound 6005

Compounds 6004 and 6005 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

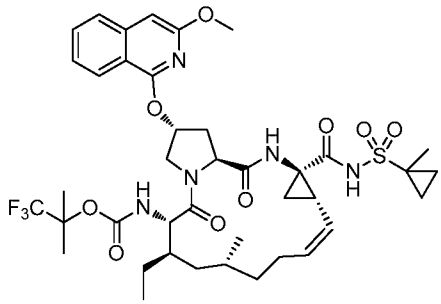
Compound 6004: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 782.4 (M^++1).

Compound 6005: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, METHANOL-d_4) δ 8.07 (d, *J*=8.5 Hz, 1H), 7.65 (d, *J*=8.2 Hz, 1H), 7.56 (t, *J*=7.5 Hz, 1H), 7.25 (t, *J*=7.5 Hz, 1H), 6.62 (s, 1H), 5.91 (br. s., 1H), 5.62 - 5.45 (m, 1H), 5.09 (m, 1H), 4.79 (d, *J*=11.6 Hz, 1H), 4.61 (dd, *J*=9.8, 7.3 Hz, 1H), 4.21 - 4.03 (m, 2H), 3.99 (s, 3H), 2.77 (dd, *J*=13.6, 7.2 Hz, 1H), 2.66 (d, *J*=8.2 Hz, 1H), 2.54 - 2.31 (m, 2H), 2.03 - 1.83 (m, 2H), 1.73 (dd, *J*=8.2, 5.5 Hz, 1H), 1.65 - 1.44 (m, 9H), 1.43 - 1.30 (m, 2H), 1.17 (s, 9H), 1.28 - 1.04 (m, 2H), 0.99 (d, *J*=7.0 Hz, 3H), 0.84 (m, 5H); MS: MS *m/z* 782.4 (M^++1).

Preparation of Compound 6006 and Compound 6007



Compound 6006



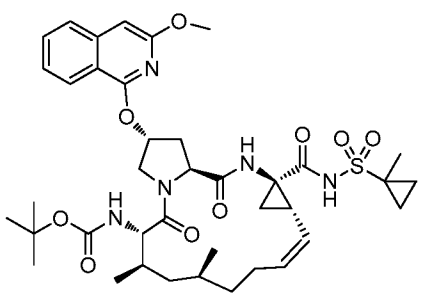
Compound 6007

Compounds 6006 and 6007 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

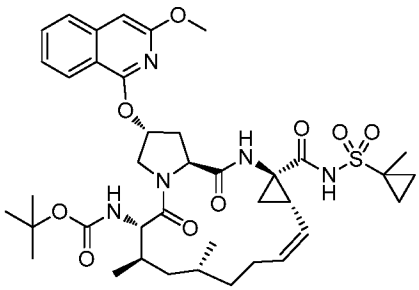
Compound 6006: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 836.4 (M^++1).

Compound 6007: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, METHANOL-d_4) δ 8.06 (d, *J*=8.2 Hz, 1H), 7.66 (d, *J*=8.5 Hz, 1H), 7.56 (t, *J*=7.5 Hz, 1H), 7.27 (t, *J*=7.5 Hz, 1H), 6.63 (s, 1H), 5.89 (br. s., 1H), 5.56 (m, 1H), 5.17 (m, 1H), 4.81 (d, *J*=11.3 Hz, 1H), 4.64 (dd, *J*=10.1, 7.3 Hz, 1H), 4.13 - 4.03 (m, 2H), 4.00 (s, 3H), 2.77 (m, 1H), 2.64 (q, *J*=9.1 Hz, 1H), 2.52 - 2.33 (m, 2H), 2.03 - 1.87 (m, 2H), 1.74 (m, 1H), 1.64 - 1.26 (m, 15H), 1.10 (t, *J*=11.7 Hz, 1H), 1.02 - 0.93 (m, 6H), 0.83 (m, 5H); MS: MS *m/z* 836.4 (M^++1).

Preparation of Compound 6008 and Compound 6009



Compound 6008



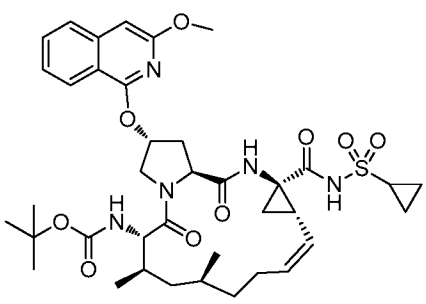
Compound 6009

Compounds 6008 and 6009 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

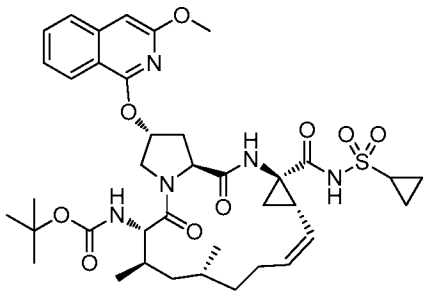
Compound 6008: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 768.3 (M^++1).

Compound 6009: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br.s, 1H), 9.10 (br. s., 1H), 8.04 (d, *J*=8.2 Hz, 1H), 7.75 (d, *J*=8.2 Hz, 1H), 7.64 (t, *J*=7.6 Hz, 1H), 7.29 (t, *J*=7.6 Hz, 1H), 7.21 (d, *J*=7.9 Hz, 1H), 6.71 (s, 1H), 5.81 (br. s., 1H), 5.53 (m, 1H), 4.98 (t, *J*=9.9 Hz, 1H), 4.64 (d, *J*=11.3 Hz, 1H), 4.54 - 4.38 (m, 1H), 4.02 - 3.85 (m, 1H), 3.92 (s, 3H), 3.80 - 3.67 (m, 1H), 2.80 - 2.59 (m, 2H), 2.41 - 2.22 (m, 2H), 1.92-1.27(m, 11H), 1.29 (d, *J*=10.7 Hz, 1H), 1.15 (s, 9H), 1.05 (m, 1H), 0.96 - 0.85 (m, 8H), 0.75 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 768.3 (M^++1).

Preparation of Compound 6010 and Compound 6011



Compound 6010



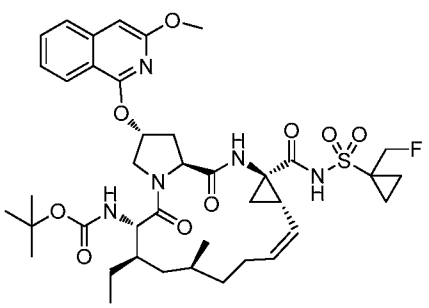
Compound 6011

Compounds 6010 and 6011 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

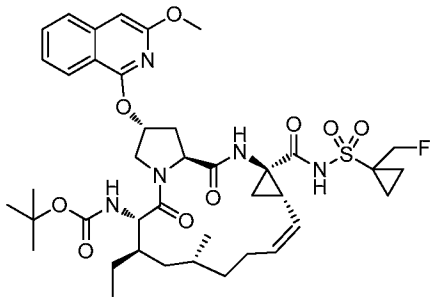
Compound 6010: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 754.3 (M^++1).

Compound 6011: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (br. s., 1H), 8.97 (br. s., 1H), 8.04 (d, *J*=8.2 Hz, 1H), 7.74 (d, *J*=8.2 Hz, 1H), 7.63 (t, *J*=7.6 Hz, 1H), 7.29 (t, *J*=7.5 Hz, 1H), 7.20 (d, *J*=7.6 Hz, 1H), 6.71 (s, 1H), 5.79 (br. s., 1H), 5.05 (m, 1H), 4.63 (m, 1H), 4.44 (m, 1H), 3.92 (m, 5H), 3.78 - 3.69 (m, 1H), 2.91 (m, 1H), 2.38 - 2.26 (m, 2H), 1.92-1.37 (m, 6H), 1.17 (s, 9H), 1.16-1.05 (m, 4H), 1.04 (m, 2H), 0.94 (d, *J*=7.0 Hz, 4H), 0.89 (d, *J*=6.4 Hz, 4H), 0.73 (t, *J*=11.9 Hz, 1H); MS: MS *m/z* 754.3 (M^++1).

Preparation of Compound 6012 and Compound 6013



Compound 6012



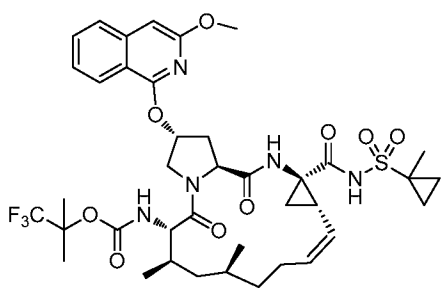
Compound 6013

Compounds 6012 and 6013 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

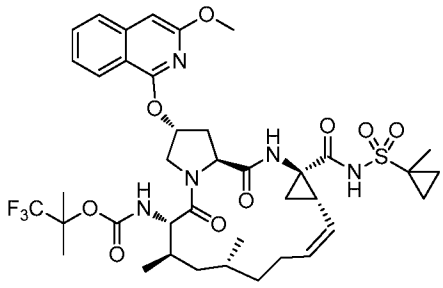
Compound 6012: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 786.4 (M^++1).

Compound 6013: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (br. s., 1H), 8.97 (br. s., 1H), 8.04 (d, *J*=8.2 Hz, 1H), 7.74 (d, *J*=8.2 Hz, 1H), 7.63 (t, *J*=7.6 Hz, 1H), 7.29 (t, *J*=7.5 Hz, 1H), 7.20 (d, *J*=7.6 Hz, 1H), 6.71 (s, 1H), 5.79 (br. s., 1H), 5.05 (m, 1H), 4.63 (m, 1H), 4.44 (m, 1H), 3.92 (m, 5H), 3.78 - 3.69 (m, 1H), 2.38 - 2.26 (m, 2H), 1.92-1.25 (m, 13H), 1.17 (s, 9H), 1.04 (m, 1H), 0.94 (d, *J*=7.0 Hz, 4H), 0.89 (d, *J*=6.4 Hz, 4H), 0.73 (t, *J*=11.9 Hz, 1H); MS: MS *m/z* 786.4 (M^++1).

Preparation of Compound 6014 and Compound 6015



Compound 6014



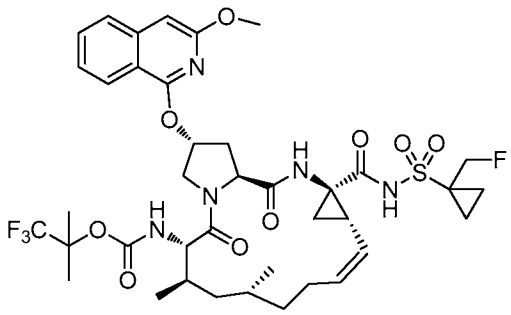
Compound 6015

Compounds 6014 and 6015 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6014: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 822.3 (M^++1).

Compound 6015: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br.s, 1H), 9.14 (br.s, 1H), 8.01 (d, *J*=8.2 Hz, 1H), 7.85 (d, *J*=7.9 Hz, 1H), 7.75 (d, *J*=8.2 Hz, 1H), 7.64 (t, *J*=7.6 Hz, 1H), 7.32 (t, *J*=7.6 Hz, 1H), 6.72 (s, 1H), 5.81 (br. s., 1H), 5.59 - 5.49 (m, 1H), 4.98 (t, *J*=9.8 Hz, 1H), 4.65 - 4.48 (m, 2H), 3.98 - 3.89 (m, 4H), 3.72 (m, 1H), 2.73 - 2.64 (m, 2H), 2.39 - 2.29 (m, 2H), 1.96 - 1.80 (m, 2H), 1.75 - 1.59 (m, 2H), 1.53 (m, 1H), 1.49 - 1.40 (m, 6H), 1.35 (s, 3H), 1.30 (m, 1H), 1.14 (m, 1H), 1.08 (s, 3H), 0.94 (d, *J*=7.0 Hz, 4H), 0.90 (d, *J*=6.4 Hz, 4H), 0.77 (t, *J*=12.7 Hz, 1H); MS: MS *m/z* 822.3 (M^++1).

Preparation of Compound 6016

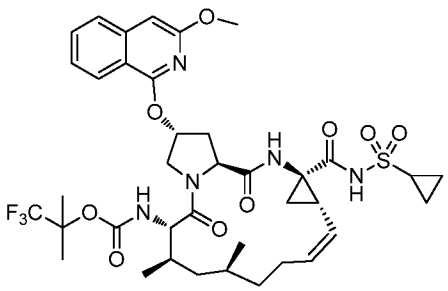


Compound 6016

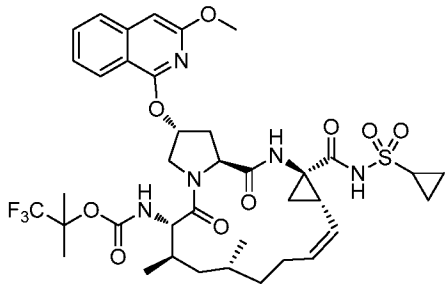
Compound 6016 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6016 : 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (br.s, 1H), 9.05 (br. s., 1H), 8.01 (d, *J*=8.2 Hz, 1H), 7.85 (d, *J*=7.9 Hz, 1H), 7.76 (d, *J*=8.5 Hz, 1H), 7.64 (t, *J*=7.6 Hz, 1H), 7.32 (t, *J*=7.6 Hz, 1H), 6.72 (s, 1H), 5.80 (br. s., 1H), 5.52 (m, 1H), 5.01 (t, *J*=9.8 Hz, 1H), 4.87-4.76 (m, 1H), 4.59-4.49 (m, 3H), 3.98 - 3.90 (m, 4H), 3.72 (m, 1H), 2.70 - 2.62 (m, 2H), 2.39 - 2.26 (m, 2H), 1.94 - 1.81 (m, 2H), 1.70 (d, *J*=6.1 Hz, 1H), 1.54 (m, 4H), 1.48 - 1.33 (m, 6H), 1.31 - 1.20 (m, 2H), 1.11 (s, 3H), 0.97 - 0.87 (m, 6H), 0.76 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 840.4 (M^++1).

Preparation of Compound 6017 and Compound 6018



Compound 6017



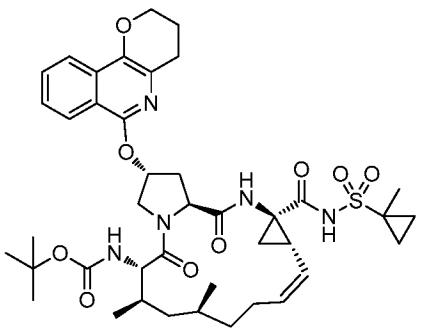
Compound 6018

Compounds 6017 and 6018 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

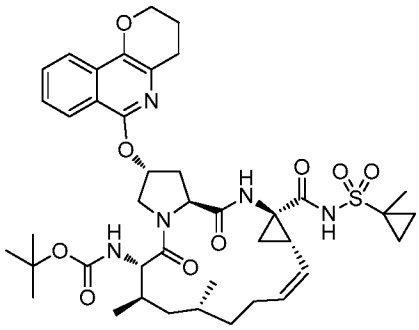
Compound 6017: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 808.3 (M^++1).

Compound 6018: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate ^{1}H NMR (500MHz, DMSO-d_6) δ 11.20 (br.s, 1H), 9.01 (br. s., 1H), 8.01 (d, *J*=8.5 Hz, 1H), 7.85 (d, *J*=7.6 Hz, 1H), 7.75 (d, *J*=8.2 Hz, 1H), 7.63 (t, *J*=7.6 Hz, 1H), 7.32 (t, *J*=7.6 Hz, 1H), 6.72 (s, 1H), 5.80 (br. s., 1H), 5.53 (m, 1H), 5.06 (t, *J*=9.3 Hz, 1H), 4.58 (d, *J*=11.3 Hz, 1H), 4.54 - 4.42 (m, 1H), 3.93 (s, 3H), 3.92 (m, 1H), 3.72 (dd, *J*=10.7, 7.9 Hz, 1H), 2.97 - 2.89 (m, 1H), 2.68 (d, *J*=8.2 Hz, 2H), 2.40 - 2.27 (m, 2H), 1.97 - 1.80 (m, 2H), 1.71 (m, 1H), 1.61 (m, 2H), 1.56 (m, 1H), 1.43 (m, 1H), 1.37 (s, 3H), 1.19 - 0.97 (m, 8H), 0.96 - 0.87 (m, 6H), 0.75 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 808.3 (M^++1).

Preparation of Compound 6019 and Compound 6020



Compound 6019



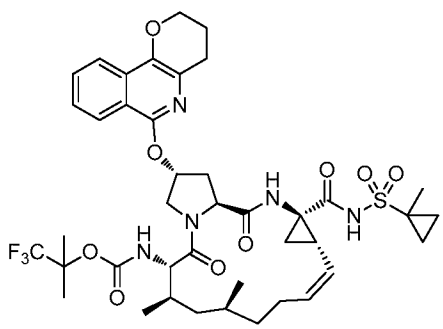
Compound 6020

Compounds 6019 and 6020 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

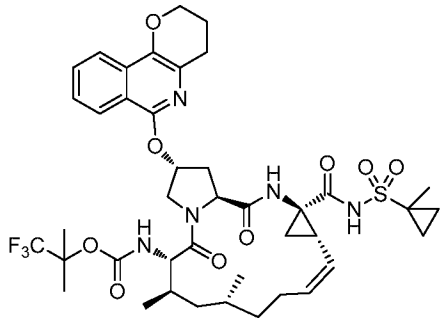
Compound 6019: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 794.5 (M^++1).

Compound 6020: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate ^{1}H NMR (500MHz, METHANOL-d_4) δ 8.10 (d, *J*=8.5 Hz, 1H), 7.97 (d, *J*=8.5 Hz, 1H), 7.65 (t, *J*=7.6 Hz, 1H), 7.44 (t, *J*=7.6 Hz, 1H), 5.83 (br. s., 1H), 5.55 (td, *J*=10.1, 5.8 Hz, 1H), 5.14 - 5.00 (m, 1H), 4.69 (d, *J*=11.6 Hz, 1H), 4.60 (dd, *J*=9.9, 7.2 Hz, 1H), 4.35 - 4.24 (m, 2H), 4.03 (dd, *J*=11.6, 3.4 Hz, 1H), 3.90 (d, *J*=10.7 Hz, 1H), 2.97 - 2.86 (m, 2H), 2.77 - 2.66 (m, 2H), 2.40 (m, 2H), 2.19 - 2.13 (m, 2H), 1.94 (m, 1H), 1.89 - 1.69 (m, 3H), 1.65 - 1.59 (m, 1H), 1.57 - 1.36 (m, 6H), 1.28 - 1.19 (m, 1H), 1.16 (s, 9H), 1.06 (m, 1H), 0.99 (t, *J*=6.9 Hz, 6H), 0.90 - 0.78 (m, 3H); MS: MS *m/z* 794.5 (M^++1).

Preparation of Compound 6021 and Compound 6022



Compound 6021



Compound 6022

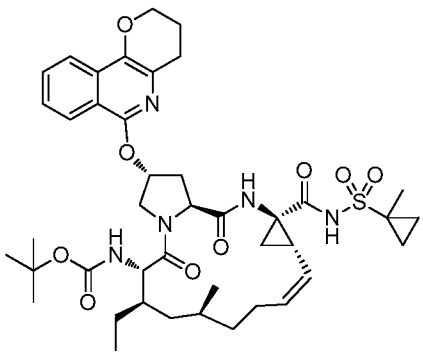
Compounds 6021 and 6022 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6021: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

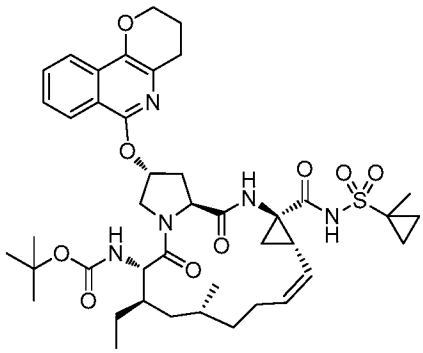
1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 848.5 (M^++1).

Compound 6022: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.10 (br. s., 1H), 8.05 (d, *J*=8.2 Hz, 1H), 7.95 (d, *J*=8.5 Hz, 1H), 7.84 (d, *J*=7.9 Hz, 1H), 7.74 (t, *J*=7.6 Hz, 1H), 7.52 (t, *J*=7.6 Hz, 1H), 5.74 (br. s., 1H), 5.53 (m, 1H), 4.98 (m, 1H), 4.59 - 4.41 (m, 2H), 4.27 (t, *J*=4.6 Hz, 2H), 3.97 - 3.87 (m, 1H), 3.74 (dd, *J*=10.7, 8.2 Hz, 1H), 2.88 (t, *J*=6.4 Hz, 2H), 2.75 - 2.67 (m, 1H), 2.63 (dd, *J*=13.1, 6.7 Hz, 1H), 2.40 - 2.21 (m, 2H), 2.16 - 2.05 (m, 2H), 1.95 - 1.79 (m, 2H), 1.75 - 1.67 (m, 1H), 1.61 (m, 1H), 1.51-1.25 (m, 12H), 1.16 (s, 3H), 0.92 (m, 8H), 0.76 (t, *J*=12.7 Hz, 1H); MS: MS *m/z* 848.5 (M^++1).

Preparation of Compound 6023 and Compound 6024



Compound 6023



Compound 6024

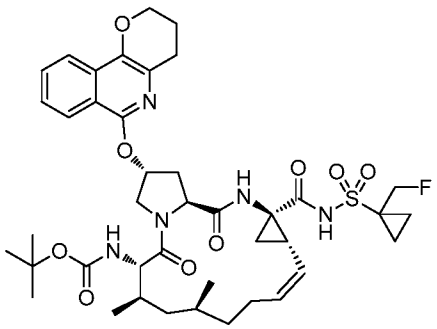
Compounds 6023 and 6024 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6023: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 808.6 (M^++1).

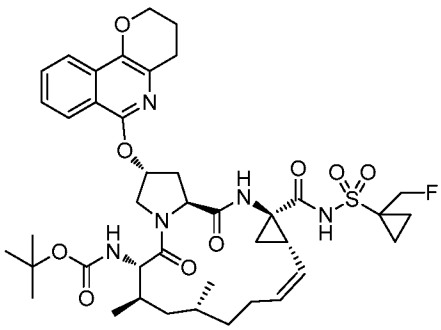
Compound 6024: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-

methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400MHz, METHANOL-d_4) δ 8.08 (d, *J*=8.0 Hz, 1H), 7.97 (d, *J*=8.3 Hz, 1H), 7.70 - 7.59 (m, 1H), 7.51 - 7.37 (m, 1H), 5.84 (br. s., 1H), 5.53 (td, *J*=9.9, 6.0 Hz, 1H), 5.04 (br. s., 1H), 4.73 (d, *J*=11.3 Hz, 1H), 4.59 (dd, *J*=10.0, 7.3 Hz, 1H), 4.36 - 4.23 (m, 2H), 4.13 (d, *J*=11.3 Hz, 1H), 4.03 (dd, *J*=11.5, 3.5 Hz, 1H), 3.03 - 2.84 (m, 2H), 2.79 - 2.61 (m, 2H), 2.40 (ddd, *J*=13.8, 9.9, 4.1 Hz, 2H), 2.22 - 2.12 (m, 2H), 2.01 - 1.87 (m, 2H), 1.73 (dd, *J*=8.3, 5.5 Hz, 1H), 1.67 - 0.93 (m, 25H), 0.89 - 0.79 (m, 5H); MS: MS *m/z* 808.6 (M^++1).

Preparation of Compound 6025 and Compound 6026



Compound 6025



Compound 6026

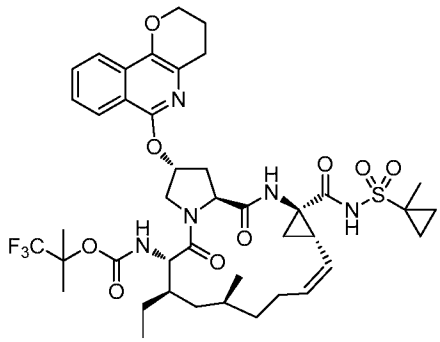
Compounds 6023 and 6024 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6023: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 812.2 (M^++1).

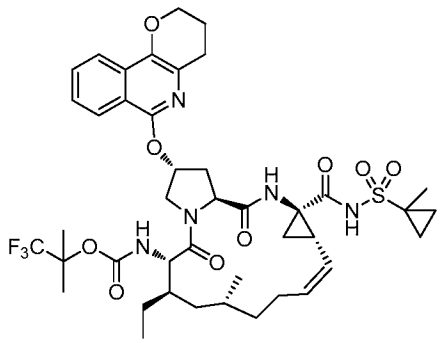
Compound 6024: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.26 (s, 1H), 8.98 (s, 1H), 8.08 (d, *J*=8.2 Hz, 1H), 7.94 (d, *J*=8.2 Hz, 1H), 7.73 (t, *J*=7.3

Hz, 1H), 7.49 (t, *J*=7.6 Hz, 1H), 7.21 (d, *J*=7.9 Hz, 1H), 5.72 (br. s., 1H), 5.51 (d, *J*=5.5 Hz, 1H), 5.00 (t, *J*=10.1 Hz, 1H), 4.85 (d, *J*=11.0 Hz, 1H), 4.75 (d, *J*=11.3 Hz, 1H), 4.63 - 4.36 (m, 3H), 4.32 - 4.23 (m, 2H), 3.99 - 3.86 (m, 1H), 3.79 - 3.65 (m, 1H), 2.88 (t, *J*=6.1 Hz, 2H), 2.74 - 2.58 (m, 2H), 2.41 - 2.21 (m, 2H), 2.15 - 2.04 (m, 2H), 1.98 - 1.64 (m, 3H), 1.53 (m, 2H), 1.47 - 1.31 (m, 2H), 1.31 - 1.00 (m, 13H), 0.97 - 0.83 (m, 6H), 0.74 (t, *J*=12.7 Hz, 1H); MS: MS *m/z* 812.2 (M^++1).

Preparation of Compound 6027 and Compound 6028



Compound 6027



Compound 6028

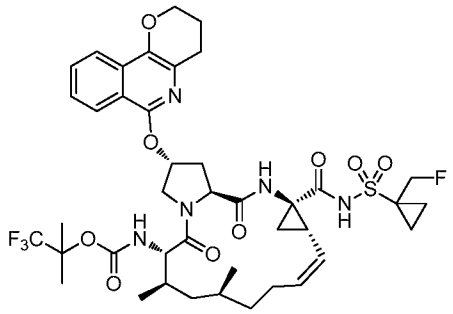
Compounds 6027 and 6028 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6027: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 862.5 (M^++1).

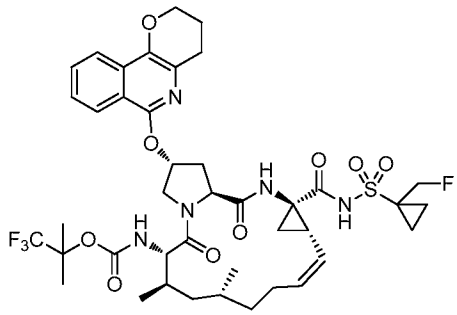
Compound 6028: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.02 (s, 1H), 9.09 (s, 1H), 8.03 (d, *J*=8.5 Hz, 1H), 7.95 (d, *J*=8.2 Hz, 1H), 7.90 (d, *J*=8.9 Hz, 1H), 7.74 (t, *J*=7.6 Hz, 1H), 7.52 (t, *J*=7.0 Hz, 1H), 5.76 (br. s., 1H), 5.54 (s, 1H), 4.98 (m, 1H), 4.59 - 4.45 (m, 2H), 4.27 (m,

2H), 4.00 - 3.86 (m, 2H), 2.88 (t, *J*=6.4 Hz, 2H), 2.76 - 2.59 (m, 2H), 2.41 - 2.25 (m, 3H), 2.11 (br. s., 2H), 2.02 - 1.90 (m, 2H), 1.61 (br. s., 1H), 1.55 - 1.37 (m, 12H), 1.30 (m, 1H), 1.16 (s, 3H), 1.03 (d, *J*=14.3 Hz, 1H), 0.97 - 0.86 (m, 6H), 0.75 (t, *J*=7.5 Hz, 3H) MS: MS *m/z* 862.5 (M^++1).

Preparation of Compound 6029 and Compound 6030



Compound 6029



Compound 6030

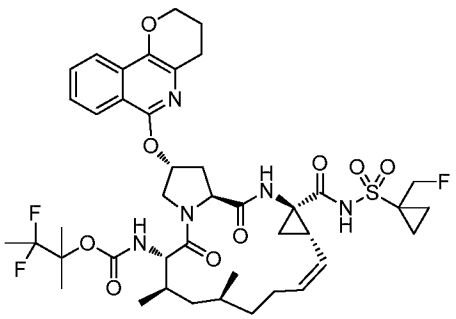
Compounds 6029 and 6030 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6029: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 866.5 (M^++1).

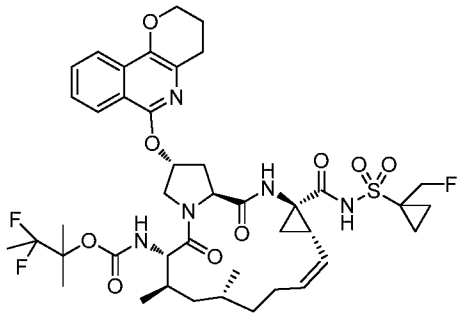
Compound 6030: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.26 (s, 1H), 9.02 (s, 1H), 8.06 (d, *J*=8.2 Hz, 1H), 7.95 (d, *J*=8.2 Hz, 1H), 7.85 (d, *J*=7.9 Hz, 1H), 7.74 (t, *J*=7.6 Hz, 1H), 7.52 (t, *J*=7.5 Hz, 1H), 5.74 (br. s., 1H), 5.57 - 5.42 (m, 1H), 5.06 - 5.00 (m, 1H), 4.90 - 4.58 (m, 1H), 4.55 - 4.44 (m, 2H), 4.27 (t, *J*=4.9 Hz, 2H), 3.92 (m, 1H), 3.80 - 3.72 (m, 2H), 2.95 - 2.84 (m, 2H), 2.72 - 2.56 (m, 2H), 2.38 - 2.23 (m, 2H), 2.16 - 2.04 (m, 2H),

1.94 - 1.81 (m, 3H), 1.74 - 1.67 (m, 1H), 1.60 - 1.48 (m, 4H), 1.43-1.10 (m, 11H), 0.98 - 0.87 (m, 5H), 0.81 - 0.71 (m, 1H); MS: MS *m/z* 866.5 (M^++1).

Preparation of Compound 6031 and Compound 6032



Compound 6031



Compound 6032

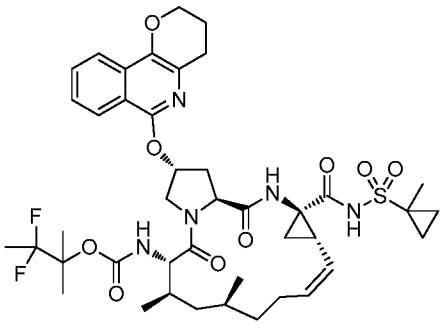
Compounds 6031 and 6032 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6031: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 862.6 (M^++1).

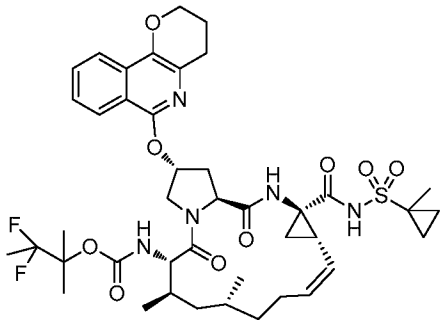
Compound 6032: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.26 (s, 1H), 8.99 (s, 1H), 8.06 (d, *J*=8.5 Hz, 1H), 7.95 (d, *J*=8.2 Hz, 1H), 7.74 (t, *J*=7.5 Hz, 1H), 7.64 (d, *J*=8.2 Hz, 1H), 7.51 (t, *J*=7.6 Hz, 1H), 5.74 (br. s., 1H), 5.52 (d, *J*=5.8 Hz, 1H), 5.01 (t, *J*=9.6 Hz, 1H), 4.89 - 4.56 (m, 1H), 4.54 - 4.42 (m, 2H), 4.32 - 4.20 (m, 2H), 3.99 - 3.88 (m, 1H), 3.80 - 3.73 (m, 1H), 2.95 - 2.84 (m, 2H), 2.77 - 2.57 (m, 2H), 2.41 - 2.23 (m, 2H), 2.14 - 2.05 (m, 2H), 1.96 - 1.49 (m, 10H), 1.46 - 1.38 (m, 2H), 1.34 (s, 3H), 1.30 - 1.15 (m, 4H), 1.12

(s, 3H), 0.93 (dd, *J*=18.2, 6.6 Hz, 6H), 0.76 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 862.6 (M^++1).

Preparation of Compound 6033 and Compound 6034



Compound 6033



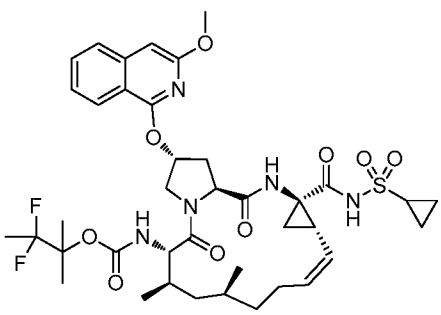
Compound 6034

Compounds 6033 and 6034 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

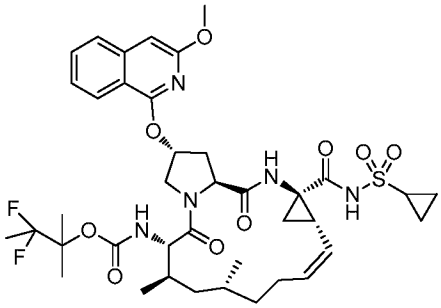
Compound 6033: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 844.6 (M^++1).

Compound 6034: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.08 (br. s., 1H), 8.06 (d, *J*=8.5 Hz, 1H), 7.95 (d, *J*=8.2 Hz, 1H), 7.74 (t, *J*=7.5 Hz, 1H), 7.63 (d, *J*=8.5 Hz, 1H), 7.51 (t, *J*=7.6 Hz, 1H), 5.74 (br. s., 1H), 5.52 (br. s., 1H), 4.98 (br. s., 1H), 4.57 - 4.41 (m, 2H), 4.27 (t, *J*=4.9 Hz, 2H), 3.99 - 3.86 (m, 1H), 3.81 - 3.69 (m, 1H), 2.91 - 2.84 (m, 2H), 2.76 - 2.59 (m, 2H), 2.41 - 2.24 (m, 2H), 2.16 - 2.08 (m, 2H), 1.97 - 1.21 (m, 18H), 1.16 (br. s., 1H), 1.09 (s, 3H), 0.92 (dd, *J*=16.2, 6.7 Hz, 8H), 0.82 - 0.72 (m, 1H) MS: MS *m/z* 844.6 (M^++1).

Preparation of Compound 6035 and Compound 6036



Compound 6035



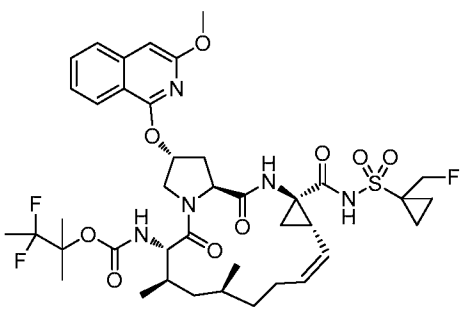
Compound 6036

Compounds 6035 and 6036 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

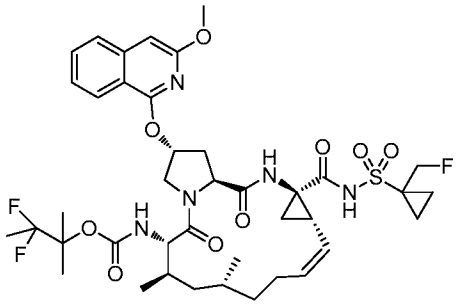
Compound 6035: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 804.5 (M^++1).

Compound 6036: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.20 (s, 1H), 8.98 (s, 1H), 8.01 (d, *J*=8.2 Hz, 1H), 7.75 (d, *J*=8.5 Hz, 1H), 7.64 (t, *J*=7.3 Hz, 2H), 7.31 (t, *J*=7.6 Hz, 1H), 6.72 (s, 1H), 5.80 (br. s., 1H), 5.58 - 5.44 (m, 1H), 5.06 (t, *J*=9.9 Hz, 1H), 4.58 (d, *J*=12.5 Hz, 1H), 4.51 - 4.44 (m, 1H), 4.11 (d, *J*=5.2 Hz, 1H), 3.95 (br. s., 1H), 3.82 - 3.70 (m, 1H), 3.18 (d, *J*=5.2 Hz, 1H), 2.97 - 2.86 (m, 1H), 2.76 - 2.63 (m, 2H), 2.40 - 2.27 (m, 2H), 1.98 - 1.66 (m, 4H), 1.65 - 1.51 (m, 4H), 1.50 - 1.35 (m, 2H), 1.28 (s, 3H), 1.20 - 1.07 (m, 5H), 1.06 - 0.99 (m, 4H), 0.93 (dd, *J*=19.5, 6.7 Hz, 6H), 0.76 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 804.5 (M^++1).

Preparation of Compound 6037 and Compound 6038



Compound 6037



Compound 6038

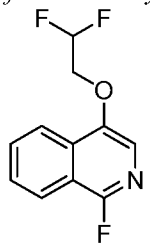
Compounds 6037 and 6038 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6037: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 836.5 (M^++1).

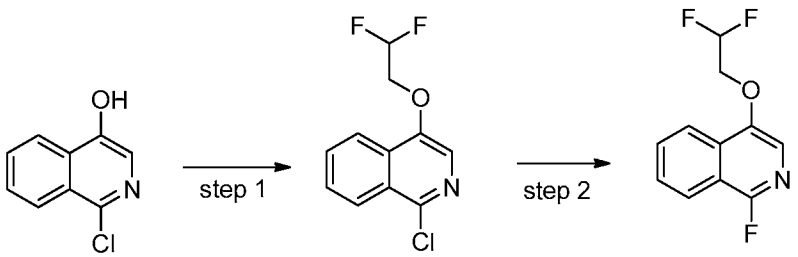
Compound 6038: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.03 (s, 1H), 8.02 (d, *J*=8.2 Hz, 1H), 7.75 (d, *J*=8.2 Hz, 1H), 7.67 - 7.60 (m, 2H), 7.31 (t, *J*=7.6 Hz, 1H), 6.72 (s, 1H), 5.81 (br. s., 1H), 5.59 - 5.44 (m, 1H), 5.01 (t, *J*=10.1 Hz, 1H), 4.91 - 4.72 (m, 1H), 4.65 - 4.55 (m, 1H), 4.49 (t, *J*=10.1 Hz, 1H), 4.02 - 3.84 (m, 4H), 3.79 - 3.68 (m, 2H), 2.74 - 2.63 (m, 2H), 2.42 - 2.28 (m, 2H), 1.97 - 1.76 (m, 2H), 1.69 m, 2H), 1.64 - 1.50 (m, 6H), 1.49 - 1.34 (m, 2H), 1.31 - 1.12 (m, 6H), 1.04 (s, 3H), 0.92 (dd, *J*=18.5, 6.6 Hz, 6H), 0.77 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 836.5 (M^++1).

Preparation of Intermediates and Compounds for Formula 1
Section 2:

Preparation of 4-(2,2-difluoroethoxy)-1-fluoroisoquinoline:



Scheme:



Step 1:

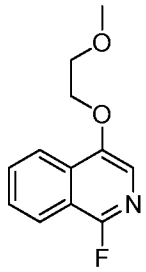
Potassium carbonate (0.462 g, 3.34 mmol) was added to a solution of 1-chloroisoquinolin-4-ol (.5 g, 2.78 mmol) and 2-bromo-1,1-difluoroethane (0.807 g, 5.57 mmol) in dry DMF (10 mL) and heated to 50 °C for overnight. Water (20 mL) and EtOAc (50mL) were added. The organic layer was washed with water 2 more times and then brine, dried over $MgSO_4$, filtered and evaporated to give the final product 1-chloro-4-(2,2-difluoroethoxy)isoquinoline (624 mg, 92% yield) as a light yellow solid. LCMS confirms product. No purification necessary. MS: MS *m/z* 244.1 (M^++1).

Step 2:

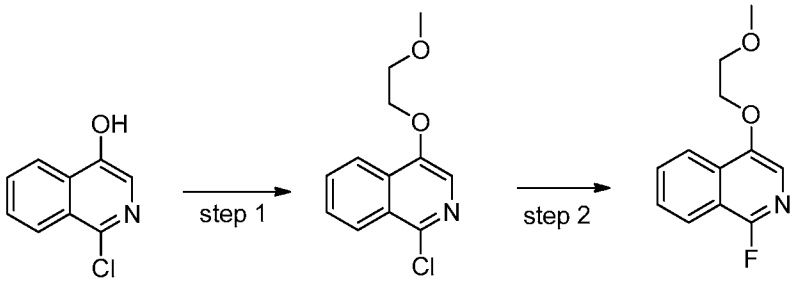
To a solution of 1-chloro-4-(2,2-difluoroethoxy)isoquinoline (630 mg, 2.59 mmol) in DMSO (10 mL) was added CsF (786 mg, 5.17 mmol) and heated to 140 °C for 2 hrs. LC/MS showed the desired product. The reaction was diluted with Ethylacteate and washed with water, and brine. The organic phase was collected, dried over sodium sulfate, and concentrated under vacuum to give the crude product which was purified by silica gel chromatography using a gradient of 5-50% EtOAc/Hexanes. The product fractions were collected and the solvent removed under vacuum to givet the

desired product 4-(2,2-difluoroethoxy)-1-fluoroisoquinoline (310 mg, 52.8% yield). MS: MS *m/z* 228.1 (M^++1).

Preparation of 1-fluoro-4-(2-methoxyethoxy)isoquinoline



Scheme:



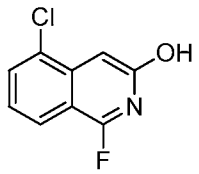
Step 1:

1-chloroisoquinolin-4-ol (.5 g, 2.78 mmol), 1-bromo-2-methoxyethane (0.318 mL, 3.34 mmol), and potassium carbonate (0.539 g, 3.90 mmol) were added to a solution of DMF (10 mL) and heated to 45 °C for 1 hr. Ater 45 min, the temp was raised to 55°C for 45 min. One half of an equivalent of 1-bromo-2-methoxyethane (0.318 mL, 3.34 mmol) was then added and then stirred at 40°C for overnight. The reaction was diluted with water and extracted with EtOAc. The organic layer was washed with brine, collected, dried over $MgSO_4$, filtered and evaporated to give the crude product. Crude material purified via silica gel chromatography(10-60% EtOAc:Hex) to give the desired product 1-chloro-4-(2-methoxyethoxy)isoquinoline (368 mg, 1.548 mmol, 55.6 % yield) as an orange solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.33 - 8.24 (m, 2H), 7.83 (s, 1H), 7.81 - 7.68 (m, 2H), 4.40 - 4.32 (m, 2H), 3.95 - 3.84 (m, 2H), 3.52 (s, 3H). MS: MS *m/z* 238.15 (M^++1).

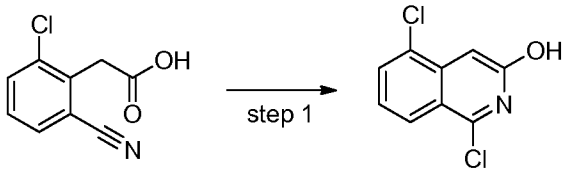
Step 2:

To a solution of 1-chloro-4-(2-methoxyethoxy)isoquinoline (368 mg, 1.548 mmol) in DMSO (7 mL) was added CsF (470 mg, 3.10 mmol) and heated to 140 °C for 2 hrs. LC/MS showed the desired product. The reaction was diluted with Ethylacteate and washed with water, and brine. The organic phase was collected, dried over sodium sulfate, and concentrated under vacuum to give the crude product which was purified by silica gel chromatography using a gradient of 5-25% EtOAc/Hexanes. The product fractions were collected and the solvent removed under vacuum to givet the desired product 1-fluoro-4-(2-methoxyethoxy)isoquinoline(241mg,70.4% yield) as a white solid. MS: MS *m/z* 222.15 (M^++1).

Preparation of 1,5-dichloroisoquinolin-3-ol



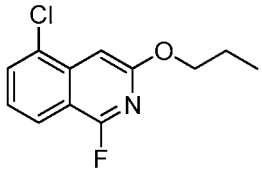
Scheme:



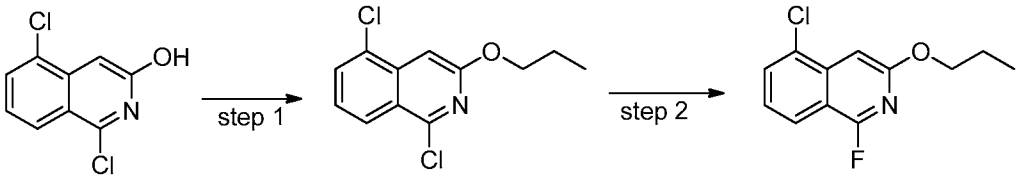
Step 1:

2-(2-chloro-6-cyanophenyl)acetic acid (10.5 g, 53.7 mmol) and $SOCl_2$ (20 mL, 274 mmol) were stirred in dichloromethane (25 mL) at RT. The suspension became a solution over 4 h. The reaction was stirred overnight. The volitile organics were removed under vacuum and the residue was taken up in DCM and filtered. The filtrate was concentrated and then dissolved in 4 N HCl dioxane (30 mL) and transfered to a sealed vessel and heated to 60 °C for 3 h. The reaction was cooled and the solid was collected, washed with dioxane, and dried under vacuum to give the product 1,5-dichloroisoquinolin-3-ol(8 g, 69.6% yield) as a solid ^{1}H NMR (400MHz, DMSO-d_6) δ 11.66 (s, 1H), 8.11 (dt, *J*=8.6, 1.0 Hz, 1H), 7.90 (dd, *J*=7.6, 1.0 Hz, 1H), 7.46 (dd, *J*=8.6, 7.6 Hz, 1H), 7.11 (d, *J*=1.0 Hz, 1H). . MS: MS *m/z* 214.08(M^++1).

Preparation of 5-chloro-1-fluoro-3-propoxyisoquinoline



Scheme:



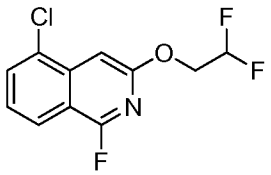
Step 1:

Potassium carbonate (646 mg, 4.67 mmol) was added to a solution of 1,5-dichloroisoquinolin-3-ol (500 mg, 2.336 mmol) and 1-bromopropane (0.234 mL, 2.57 mmol) and heated to 50 °C for 3 hrs. After 3 hours the reaction was diluted with water and extracted with EtOAc (2X). The organic layer was washed with water followed by brine, dried over $MgSO_4$, filtered and evaporated to give the crude product 1,5-dichloro-3-propoxyisoquinoline(550mg, 92% yield), which was used as is in the next step. MS: MS *m/z* 256.1(M^++1).

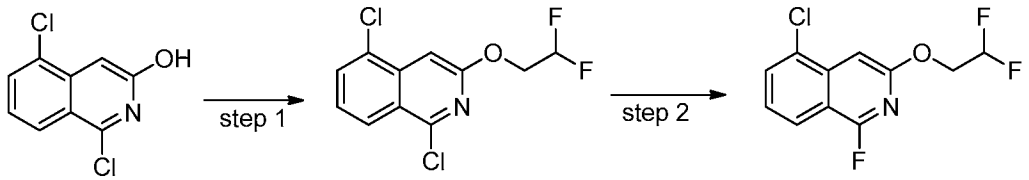
Step 2:

To a solution of 1,5-dichloro-3-propoxyisoquinoline (565 mg, 2.206 mmol)in DMSO (5 mL) was added CsF (369 mg, 2.427 mmol) and heated to 140 °C for 2 hrs. LC/MS showed the desired product. The reaction was diluted with Ethylacteate and washed with water, and brine. The organic phase was collected, dried over $MgSO_4$, and concentrated under vacuum to give the crude product as a reddish brown solid. Crude material purified via silica gel chromatography (90g column; 0-40% EtOAc:Hex) to get the product 5-chloro-1-fluoro-3-propoxyisoquinoline(440mg, 83% yield) as a yellow solid. MS: MS *m/z* 240.05(M^++1).

Preparation of 5-chloro-3-(2,2-difluoroethoxy)-1-fluoroisoquinoline



Scheme:



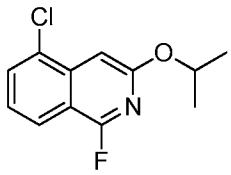
Step 1:

Potassium carbonate (646 mg, 4.67 mmol) was added to a solution of 1,5-dichloroisoquinolin-3-ol (500 mg, 2.336 mmol) and 2-bromo-1,1-difluoroethane (677 mg, 4.67 mmol) and heated to 50 °C for 18 hrs. The reaction was diluted with water and extracted with EtOAc. The organic layer was washed with water (2X) followed by brine. The organic layer was collected, dried over $MgSO_4$, filtered and evaporated to give the crude product 1,5-dichloro-3-(2,2-difluoroethoxy)isoquinoline(590mg, 90% yield) which was used as is in the next step. MS: MS *m/z* 278.1(M^++1).

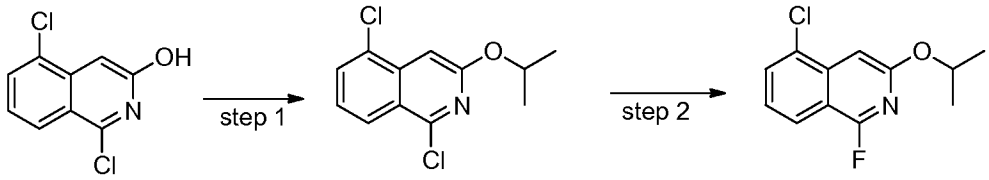
Step 2:

To a solution of 1,5-dichloro-3-(2,2-difluoroethoxy)isoquinoline (581 mg, 2.089 mmol) in DMSO (5 mL) was added CsF (349 mg, 2.298 mmol) and heated to 140 °C for 2 hrs. LC/MS showed the desired product. The reaction was diluted with ethyl acteate and washed with water, and brine. The organic phase was collected, dried over $MgSO_4$, and concentrated under vacuum to give the crude product as a reddish brown solid. Crude material purified via silica gel chromatography (90g column; 0-40% EtOAc:Hex) to get the product 5-chloro-3-(2,2-difluoroethoxy)-1-fluoroisoquinoline(450mg, 82% yield) as a yellow solid. MS: MS *m/z* 262.1(M^++1).

Preparation of 5-chloro-1-fluoro-3-isopropoxyisoquinoline



Scheme:



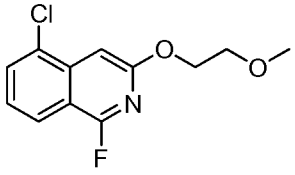
Step 1:

Sodium hydride (103 mg, 2.57 mmol) was added to a solution of 1,5-dichloroisoquinolin-3-ol (500 mg, 2.336 mmol) and 2-bromopropane (575 mg, 4.67 mmol) and stirred at rt for 3 hrs. The reaction was diluted with water and extracted with EtOAc. The organic layer was washed with water (2X) followed by brine. The organic layer was collected, dried over $MgSO_4$, filtered and evaporated to give the crude product 1,5-dichloro-3-isopropoxyisoquinoline(598mg, 100% yield) which was used as is in next step. MS: MS *m/z* 256.1(M^++1).

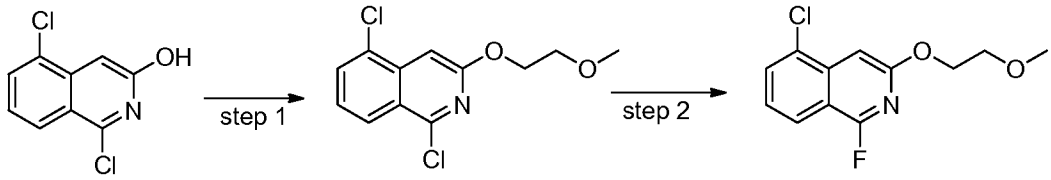
Step 2:

To a solution of 1,5-dichloro-3-isopropoxyisoquinoline (598 mg, 2.335 mmol)in DMSO (5 mL) was added CsF (390 mg, 2.57 mmol) and heated to 140 °C for 2 hrs. LC/MS showed the desired product. The reaction was diluted with ethyl acteate and washed with water, and brine. The organic phase was collected, dried over $MgSO_4$, and concentrated under vacuum to give the crude product as a reddish brown solid. Crude material purified via silica gel chromatography (90g column; 0-40% EtOAc:Hex) to get the product 5-chloro-1-fluoro-3-isopropoxyisoquinoline(520mg, 93% yield) as a yellow solid. MS: MS *m/z* 240.15(M^++1).

Preparation of 5-chloro-1-fluoro-3-(2-methoxyethoxy)isoquinoline



Scheme:



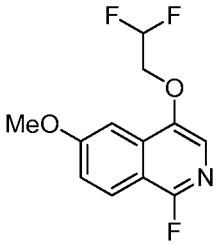
Step 1:

Potassium carbonate (646 mg, 4.67 mmol) was added to a solution of 1,5-dichloroisoquinolin-3-ol (500 mg, 2.336 mmol) and 1-bromo-2-methoxyethane (357 mg, 2.57 mmol) and heated to 50 °C for 3 hrs. After 3 hrs the reaction was diluted with water and extracted with EtOAc (2X). The organic layer was washed with water followed by brine, dried over $MgSO_4$, filtered and evaporated to give the crude product 1,5-dichloro-3-(2-methoxyethoxy)isoquinoline(550mg, 87% yield), which was used as is in the next step. MS: MS *m/z* 272.1(M^++1).

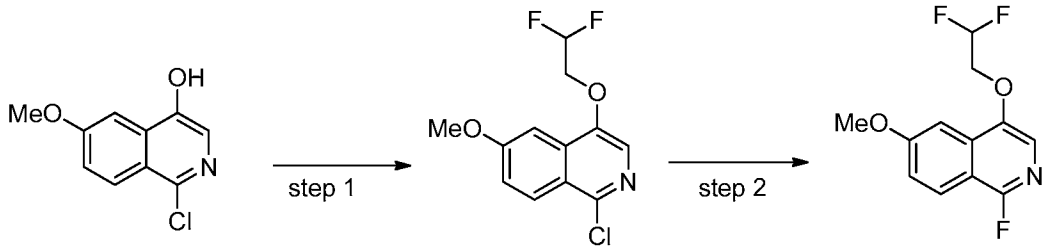
Step 2:

To a solution of 1,5-dichloro-3-(2-methoxyethoxy)isoquinoline (578 mg, 2.124 mmol) in DMSO (5 mL) was added CsF (323 mg, 2.124 mmol) and heated to 140 °C for 2 hrs. LC/MS showed the desired product. The reaction was diluted with ethyl acteate and washed with water, and brine. The organic phase was collected, dried over $MgSO_4$, and concentrated under vacuum to give the crude product as a reddish brown solid. Crude product purified via biotage (90g column, 5-50% EtAOc:Hex) to give the product 5-chloro-1-fluoro-3-(2-methoxyethoxy)isoquinoline (250mg, 46% yield) as a light yellow solid. MS: MS *m/z* 256.15(M^++1).

Preparation of 4-(2,2-difluoroethoxy)-1-fluoro-6-methoxyisoquinoline



Scheme:



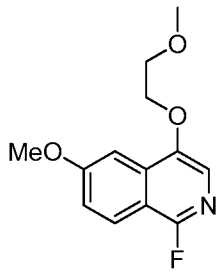
Step 1:

Potassium carbonate (659 mg, 4.77 mmol) was added to a solution of 1-chloro-6-methoxyisoquinolin-4-ol (500 mg, 2.385 mmol) and 2-bromo-1,1-difluoroethane (346 mg, 2.385 mmol) and stirred for 3 hrs at 50 °C. After 3 hrs, the reaction was diluted with water and extracted with EtOAc. The organic layer was washed with water(2X) followed by brine. The organic layer was collected, dried over $MgSO_4$, filtered and evaporated to give the crude product 1-chloro-4-(2,2-difluoroethoxy)-6-methoxyisoquinoline(538 mg, 82%) as an orange solid. Crude material used as is in next step. MS: MS *m/z* 274.1(M^++1).

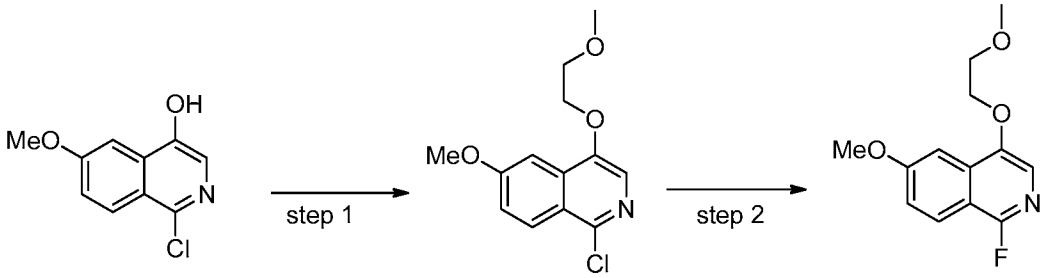
Step 2:

To a solution of 1-chloro-4-(2,2-difluoroethoxy)-6-methoxyisoquinoline (538 mg, 1.966 mmol) in DMSO (5 mL) was added CsF (597 mg, 3.93 mmol) and heated to 140 °C for 2 hrs. LC/MS showed the desired product. The reaction was diluted with ethyl acteate and washed with water, and brine. The organic phase was collected, dried over $MgSO_4$, and concentrated under vacuum to give the crude product as a reddish brown solid. The crude material was purified via silica gel chromatography (5-50% EtOAc:Hex) to give the product 4-(2,2-difluoroethoxy)-1-fluoro-6-methoxyisoquinoline (237 mg, 0.921 mmol, 46.9 % yield) as a light yellow solid. MS: MS *m/z* 258.2(M^++1).

Preparation of 1-fluoro-6-methoxy-4-(2-methoxyethoxy)isoquinoline



Scheme:



Step 1:

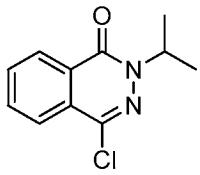
Potassium carbonate (659 mg, 4.77 mmol) was added to a solution of 1-chloro-6-methoxyisoquinolin-4-ol (500 mg, 2.385 mmol) and 1-bromo-2-methoxyethane (663 mg, 4.77 mmol) and stirred for 3 hrs at 50 °C. After 3 hrs, the reaction was diluted with water and extracted with EtOAc. The organic layer was washed with water(2X) followed by brine. The organic layer was collected, dried over $MgSO_4$, filtered and evaporated to give the crude product 1-chloro-6-methoxy-4-(2-methoxyethoxy)isoquinoline (560mg, 88% yield) as an orange solid. Crude material used as is in next step. MS: MS *m/z* 268.15(M^++1).

Step 2:

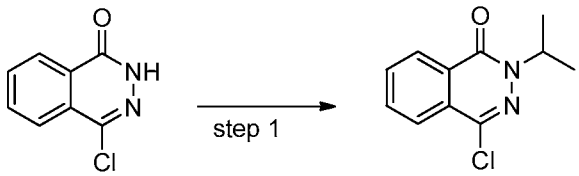
To a solution of 1-chloro-6-methoxy-4-(2-methoxyethoxy)isoquinoline (560 mg, 2.092 mmol) in DMSO (5 mL) was added CsF (636 mg, 4.18 mmol) and heated to 140 °C for 2 hrs. LC/MS showed the desired product. The reaction was diluted with Ethylacteate and washed with water, and brine. The organic phase was collected, dried over $MgSO_4$, and concentrated under vacuum to give the crude product as a reddish brown solid. The crude material was purified via silica gel chromatography (5-50% EtOAc:Hex) to give the product 1-fluoro-6-methoxy-4-(2-

methoxyethoxy)isoquinoline (168 mg, 0.669 mmol, 32.0 % yield) as a light yellow solid. MS: MS *m/z* 252.2(M^++1).

Preparation of 4-chloro-2-isopropylphthalazin-1(2H)-one



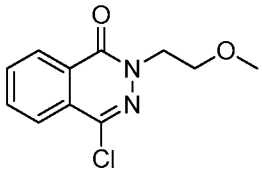
Scheme:



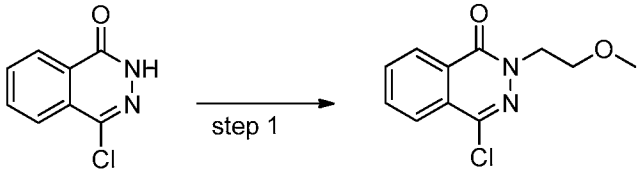
Step 1:

Potassium carbonate (459 mg, 3.32 mmol) was added to a solution of 4-chlorophthalazin-1(2H)-one (300 mg, 1.661 mmol) and 2-bromopropane (409 mg, 3.32 mmol) and heated to 50 °C for 3 hrs. After 3 hrs the reaction was diluted with water and extracted with EtOAc (2X). The organic layer was washed with water followed by brine, dried over $MgSO_4$, filtered and evaporated to give the crude product 4-chloro-2-isopropylphthalazin-1(2H)-one(380mg, 103% yield) , which was used as is in the next step. MS: MS *m/z* 223.15(M^++1).

Preparation of 4-chloro-2-(2-methoxyethyl)phthalazin-1(2H)-one



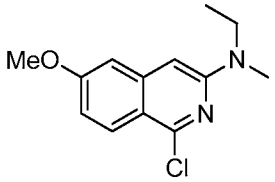
Scheme:



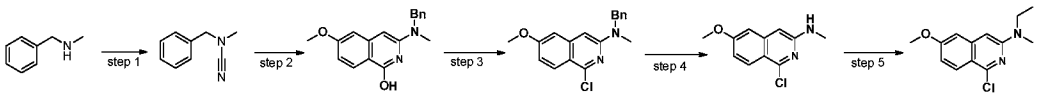
Step 1:

Potassium carbonate (459 mg, 3.32 mmol) was added to a solution of 4-chlorophthalazin-1(2H)-one (300 mg, 1.661 mmol) and 1-bromo-2-methoxyethane (462 mg, 3.32 mmol) and heated to 50 °C for 3 hrs. After 3 hrs the reaction was diluted with water and extracted with EtOAc (2X). The organic layer was washed with water followed by brine, dried over $MgSO_4$, filtered and evaporated to give the crude product. The crude material was purified via silica gel chromatography (90g column, 5-45% EtOAc:Hex) to give the desired product 4-chloro-2-(2-methoxyethyl)phthalazin-1(2H)-one(280 mg, 70.6% yield) as a yellow solid. MS: MS *m/z* 223.15(M^++1).

Preparation of 1-chloro-N-ethyl-6-methoxy-N-methylisoquinolin-3-amine



Scheme:



Step 1:

To a solution of N-methyl-1-phenylmethanamine (5.31 mL, 41.3 mmol) and Hunig'sBase (7.93 mL, 45.4 mmol) in THF (110 mL) at 0 °C was added cyanic bromide (4.81 g, 45.4 mmol) in one pot. The reaction was stirred at 0 °C for 2 hr before allowing to warm up to RT for 16 hrs.

The reaction was concentrated under vacuum, and the residue was suspended in ethyl acetate. The resulting mixture was filtered, and the filtrate was washed with water(X2) and brine, dried over anhyd. sodium sulfate, filtered, and concentrated to afford N-benzyl-N-methylcyanamide (5.8 g, 39.7 mmol, 96 % yield) as a light yellow thin oil. All aqueous workup solutions and any equipment using cyanic bromide were soaked in bleach and then washed with water. All bleach material put in cubitainer and properly labelled for disposal. MS: MS *m/z* 147.1(M^++1). ^1H NMR (500MHz, CHLOROFORM-d) δ 7.44 - 7.34 (m, 5H), 4.18 (s, 2H), 2.80 (s, 3H).

Step 2:

To a solution of N,N-diethyl-4-methoxy-2-methylbenzamide (2 g, 9.04 mmol) in THF (50 mL) was added tert-butyllithium (7.97 mL, 13.56 mmol) dropwise at -78°C. After stirring for 0.5 h, N-benzyl-N-methylcyanamide (1.453 g, 9.94 mmol) was added, then warmed to rt, and stirred for 16 h. The reaction mixture was quenched with water (1mL) and partially evaporated to half to one third of original volume, neutralized with 1 N HCl. The solution was separated with EtOAc. Upon adding to separatory funnel a solid mass precipitated out and was filtered off and washed with water then dried under high vaccuum for overnight. The light yellow solid was the exptected product 3-(benzyl(methyl)amino)-6-methoxyisoquinolin-1-ol (1.8 g, 6.12 mmol, 67.7 % yield). MS: MS *m/z* 295.3(M^++1).

Step 3:

A solution of 3-(benzyl(methyl)amino)-6-methoxyisoquinolin-1-ol (1.8 g, 6.12 mmol) in $POCl_3$ (10 mL) was refluxed for 4 h. After concentration, the residue was taken into a mixture of 100 mL of DCM and 50 mL of water, cooled to 0°C, neutralized with 3 N NaOH, dried over $MgSO_4$,and concentrated to give N-benzyl-1-chloro-6-methoxy-N-methylisoquinolin-3-amine (1.44 g, 4.60 mmol, 75 % yield) as a yellow solid. MS: MS *m/z* 313.15(M^++1).

Step 4:

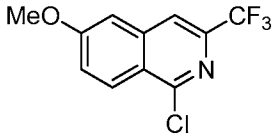
Triflic acid (4.09 mL, 46.0 mmol) was added to a solution of N-benzyl-1-chloro-6-methoxy-N-methylisoquinolin-3-amine (1.44 g, 4.60 mmol) in DCM (20 mL) at RT and stirred for 1 hr at RT before reverse adding to a solution of sat. sodium bicarbonate. The organic layer was diluted with DCM and separated. The organic layer was dried over MgSO4, filtered and evaporated. The crude material was purifed via silica gel chromatography (90g column, 0-30% EtOAc:Hex) to give the expected product 1-chloro-6-methoxy-N-methylisoquinolin-3-amine (610 mg, 2.74 mmol, 59.5 % yield) as an orange solid. MS: MS *m/z* 223.15(M^++1).

Step 5:

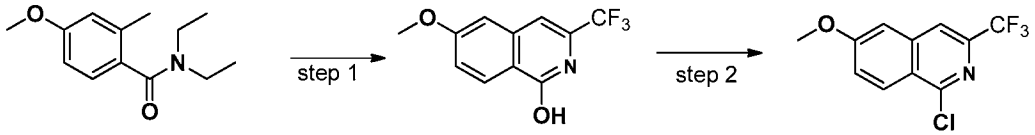
Hunig's base (0.235 mL, 1.347 mmol) was added to a solution of 1-chloro-6-methoxy-N-methylisoquinolin-3-amine (150 mg, 0.674 mmol) and acetaldehyde

(0.042 mL, 0.741 mmol) in MeOH (5 mL) and stirred for 30min . Acetic Acid (1 mL) and Cyanoborohydride, polymer supported (2 mmol/gram) (50 mg, 0.674 mmol) were then added and the reaction stirred at r.t. for 2 hrs. Reaction filtered through nylon frit filter and evaporated on rotovap to give the crude product with no purification. The material was taken up in EtOAc and washed with sat. sodium bicarbonate. The organic layer was collected, dried over $MgSO_4$, filtered and evaporated to give the expected product 1-chloro-N-ethyl-6-methoxy-N-methylisoquinolin-3-amine(140mg, 83% yield) as a dark orange solid. MS: MS *m/z* 251.15(M^++1).

Preparation of 1-chloro-6-methoxy-3-(trifluoromethyl)isoquinoline



Scheme:



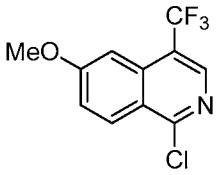
Step 1:

To a solution of N,N-diethyl-4-methoxy-2-methylbenzamide (1 g, 4.52 mmol) in THF (40 mL) was added tert-butyllithium (3.99 mL, 6.78 mmol) dropwise at -78°C. After stirring for 0.5 h, 2,2,2-trifluoroacetonitrile (0.472 g, 4.97 mmol) was bubbled through the solution via syringe for 1 minute, then warmed to rt, and stirred for 16 h. The reaction mixture was quenched with water (1mL) and partially evaporated to half to one third of original volume, neutralized with 1 N HCl. The solution was separated with EtOAc. The organics were collected, washed with brine, dried over $MgSO_4$, filtered and evaporated to give crude material as a dark yellow solid. The crude material was purified via silica gel chromatography (90g column, 10-50% EtOAc:Hex) to give the product 6-methoxy-3-(trifluoromethyl)isoquinolin-1-ol (271 mg, 1.114 mmol, 24.66 % yield) as a light yellow solid. MS: MS *m/z* 244.19(M^++1).

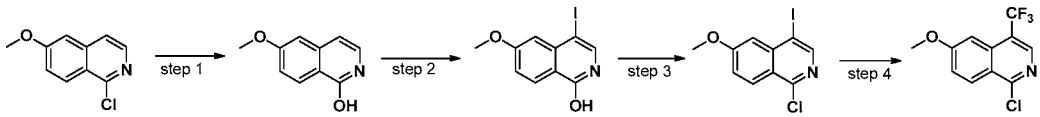
Step 2:

A solution of 6-methoxy-3-(trifluoromethyl)isoquinolin-1-ol (271 mg, 1.114 mmol) in POCl3 (3 mL) was refluxed for 4 h. After concentration, the residue was taken into a mixture of 100 mL of DCM and 50 mL of water, cooled to 0°C, neutralized with 3 N NaOH, dried over MgSO4, concentrated and purified via silica gel chromatography (5-20% EtOAc:Hex) to give the pure product 1-chloro-6-methoxy-3-(trifluoromethyl)isoquinoline (250 mg, 0.956 mmol, 86 % yield) as an orange solid. MS: MS *m/z* 262.1(M^++1).

Preparation of 1-chloro-6-methoxy-4-(trifluoromethyl)isoquinoline



Scheme:



Step 1:

1-chloro-6-methoxyisoquinoline (5 g, 25.8 mmol) was added to a solution of HCl (21.52 ml, 129 mmol) and heated to 120 °C and monitored by LCMS. The reaction was stirred at this temp for over the weekend (3 days). Reaction was cooled and material precipitated. The slurry was diluted with DCM and water and separated in a separatory funnel. The organic layer was washed with water (2X) followed by brine, dried over $MgSO_4$, filtered and evaporated to give the crude material. The crude material was purified via silica gel chromatography (240 g column, 0-15% MeOH:DCM) to give the expected product 6-methoxyisoquinolin-1-ol (2.38 g, 13.59 mmol, 52.6 % yield) as a white solid. MS: MS *m/z* 176.09(M^++1).

Step 2:

To a solution of NIS (3.31 g, 14.73 mmol) in CH_3CN (25 mL) was added 6-methoxyisoquinolin-1-ol (2.58 g, 14.73 mmol). The resulting suspension was slowly

warmed to reflux and maintained refluxing for 2h. After concentration, the residue was taken into water. The solid was collected through filter paper washing with hot water to give a crude product 4-iodo-6-methoxyisoquinolin-1-ol(3.87g, 87% yield) which was used in the next step with out further purification. MS: MS *m/z* 302(M^++1). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 16.12 (br. s., 1H), 12.86 (d, *J*=9.0 Hz, 1H), 12.34 (d, *J*=5.8 Hz, 1H), 11.89 (dd, *J*=8.8, 2.5 Hz, 1H), 11.76 (d, *J*=2.3 Hz, 1H), 8.70 - 8.62 (m, 3H).

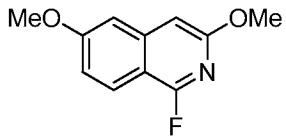
Step 3:

A solution of 4-iodo-6-methoxyisoquinolin-1-ol (2 g, 6.64 mmol) in POCl3 (10 mL) was refluxed for 4 h. After concentration, the residue was taken into a mixture of 100 mL of DCM and 50 mL of water, cooled to 0°C, neutralized with 3 N NaOH, dried over MgSO4, concentrated and purified via silica gel chromatography (5-20% EtOAc:Hex) to give the pure product 1-chloro-4-iodo-6-methoxyisoquinoline (1.3 g, 4.07 mmol, 61.2 % yield) as an orange solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.22 (d, *J*=9.3 Hz, 1H), 7.54 (dd, *J*=9.3, 2.5 Hz, 1H), 7.33 (d, *J*=2.5 Hz, 1H), 4.03 (s, 3H). MS: MS *m/z* 320(M^++1).

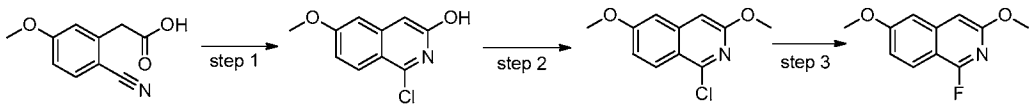
Step 4:

Copper(I) Iodide (298 mg, 1.565 mmol) and potassium fluoride (182 mg, 3.13 mmol) were weighed out in a flask and heated with a heat gun under vaccuum until the solid turned a pale yellow green. After cooling to RT dry THF (3 mL), and dry DMF (3 mL) and trimethyl(trifluoromethyl)silane (0.463 mL, 3.13 mmol) were added at RT and then heated to 60°C for 6 hrs. LCMS shows small product peak. Reaction heated for overnight. Reaction was then cooled and quenched with water added and separated with EtOAc. The organic layer was washed with brine, dried over MgSO4, filtered and evaporated to give the crude product 1-chloro-6-methoxy-4-(trifluoromethyl)isoquinoline (175 mg, 0.669 mmol, 85 % yield) which was used as is in following step. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.59 - 8.53 (m, 1H), 8.37 (d, *J*=9.3 Hz, 1H), 7.45 - 7.34 (m, 2H), 4.02 (s, 3H). MS: MS *m/z* 262.1(M^++1).

Preparation of 1-fluoro-3,6-dimethoxyisoquinoline



Scheme:



Step 1:

2-(2-cyano-5-methoxyphenyl)acetic acid (3.8 g, 19.88 mmol), and $SOCl_2$ (20 mL, 274 mmol) were stirred in dichloromethane (25 mL) at RT. The suspension became a solution over 8 h. The reaction was stirred overnight. The volitile organics were removed under vacuum and the residue was taken up in DCM and filtered. The filtrate was concentrated and then dissolved in 4 N HCl dioxane (30 mL) and transfered to a sealed vessel and heated to 60 °C for 3 h. The reaction was cooled and the solid was collected, washed with dioxane, and dried under vacuum to give the product 1-chloro-6-methoxyisoquinolin-3-ol(3.3g, 70% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.10 (d, *J*=9.6 Hz, 1H), 7.12 (dd, *J*=9.3, 2.5 Hz, 1H), 6.95 (s, 2H), 3.98 (s, 3H).

Step 2:

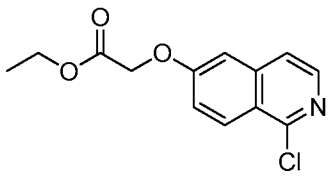
To a mixture of 1-chloro-6-methoxyisoquinolin-3-ol (3.3 g, 15.74 mmol) in DMF (30 mL) was added potassium carbonate (2.61 g, 18.89 mmol) and iodomethane (1.969 mL, 31.5 mmol). It was then stirred at rt overnight. LC/MS showed 2 peaks with the desired mass and also starting material. An additional 1 equ. of MeI, and 1 equ of K_2CO_3 was added and the reaction warmed to 40 °C for 2h. LC/MS showed all starting material had been consumed. The reaction was diluted with EtOAc and water. The organic layer was washed with water, brine, dried over sodium sulfate, and concentrated under vacuum. The crude material was pruifed by silica gel column using 20% EtOAc/Hexanes. The product fractions were collected and the solvent removed under vacuum to give the desired product 1-chloro-3,6-

dimethoxyisoquinoline(2.47g, 70% yield) as a white solid. MS: MS *m/z* 223.93(M^++1). ^{1}H NMR (400MHz, CHLOROFORM-d) d 8.10 (d, *J*=9.3 Hz, 1H), 7.08 (dd, *J*=9.3, 2.5 Hz, 1H), 6.93 (d, *J*=2.5 Hz, 1H), 6.85 (s, 1H), 4.07 - 3.99 (m, 3H), 3.95 (s, 3H).

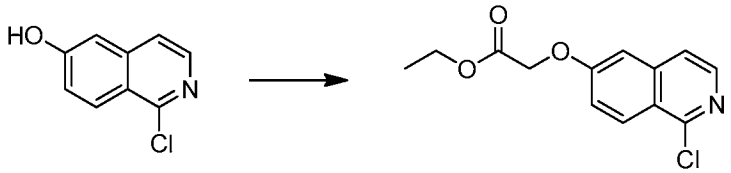
Step 3:

To a solution of 1-chloro-3,6-dimethoxyisoquinoline (300 mg, 1.341 mmol) in DMSO (5 mL) was added CsF (408 mg, 2.68 mmol) and heated to 140 °C for 2 hrs. LC/MS showed the desired product. The reaction was diluted with Ethylacteate and washed with water, and brine. The organic phase was collected, dried over $MgSO_4$, and concentrated under vacuum to give the crude product 1-fluoro-3,6-dimethoxyisoquinoline(250mg, 90% yield) as a reddish brown solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.93 (d, *J*=9.0 Hz, 1H), 7.03 (dd, *J*=9.3, 2.3 Hz, 1H), 6.95 (t, *J*=1.9 Hz, 1H), 6.75 (s, 1H), 4.01 - 3.96 (m, 3H), 3.96 - 3.90 (m, 3H). MS: MS *m/z* 208.07(M^++1).

Preparation of ethyl 2-((1-chloroisoquinolin-6-yl)oxy)acetate



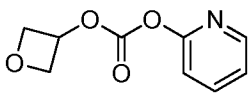
Scheme:



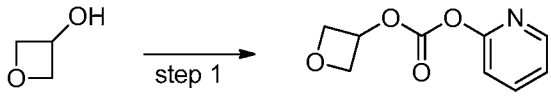
To a dry 40 mL vial equipped with a stir bar was added 1-chloroisoquinolin-6-ol (200 mg, 1.11 mmol) and potassium carbonate (231 mg, 1.67 mmol). To the vial was added dry ethyl acetate (6 mL) followed by ethyl 2-bromoacetate (0.148 mL, 1.34 mmol). The vial was sealed and then heated at 60 °C for 2h. The mixture was cooled to room temperature, diluted with acetone, and then filtered. The filtrated was concentrated and the resulting solid residue was subjected to SiO2 chromatography (hexanes:EtOAc 85:15 to 70:30) to afford ethyl 2-((1-chloroisoquinolin-6-

yl)oxy)acetate as a colorless, crystalline solid (296 mg, 66%). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.29 (d, *J*=9.3 Hz, 1H), 8.22 (d, *J*=5.8 Hz, 1H), 7.49 (d, *J*=5.8 Hz, 1H), 7.40 (dd, *J*=9.3, 2.8 Hz, 1H), 7.04 (d, *J*=2.5 Hz, 1H), 4.79 (s, 2H), 4.32 (q, *J*=7.3 Hz, 2H), 1.33 (t, *J*=7.2 Hz, 3H); MS: MS *m/z* 266.15 (M^++1).

Preparation of oxetan-3-yl pyridin-2-yl carbonate



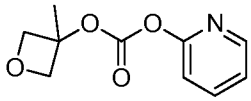
Scheme:



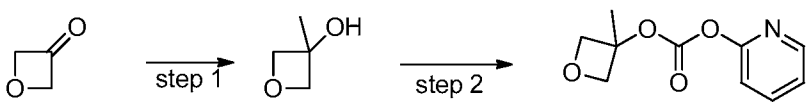
Step 1:

To a suspension of sodium hydride, 60% in mineral oil (0.594 g, 14.85 mmol) in THF (50 mL) was added oxetan-3-ol (1g, 13.50 mmol) at 0°C. After stirring 30 min, the solution was transferred to a solution of di(pyridin-2-yl) carbonate (2.92 g, 13.50 mmol) in THF (50 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. The reaction was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, concentrated to give a residue that was purified by Biotage eluting with 20-50% EtOAc in hexanes to afford the desired product oxetan-3-yl pyridin-2-yl carbonate(452mg, 17.16% yield) as an oil. 500 mg sm recovered. ^{1}H NMR (400MHz, CHLOROFORM-d) d 8.42 (dd, *J*=4.6, 1.6 Hz, 1H), 7.89 - 7.77 (m, 1H), 7.33 - 7.27 (m, 1H), 7.14 (d, *J*=8.3 Hz, 1H), 5.62 - 5.52 (m, 1H), 4.96 - 4.91 (m, 2H), 4.83 - 4.78 (m, 2H).

Preparation of 3-methyloxetan-3-yl pyridin-2-yl carbonate



Scheme:



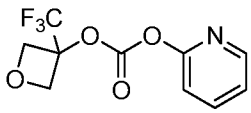
Step 1:

Methylmagnesium bromide (12.72 mL, 38.2 mmol) was added dropwise via syringe to a solution of oxetan-3-one (2.5 g, 34.7 mmol) in Diethyl ether (110 mL) at 0 °C and stirred at this temp for 1 hr before warming up to RT. The reaction was quenched with sat. ammonium chloride and extracted with ether. The organic layer was washed with brine, collected, dried over $MgSO_4$, filtered and evaporated to give the crude product 3-methyloxetan-3-ol (1.5g, 49.1% yield) as a clear oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 4.63 (d, *J*=6.5 Hz, 2H), 4.53 - 4.45 (m, 2H), 2.48 (br. s., 1H), 1.58 (s, 3H).

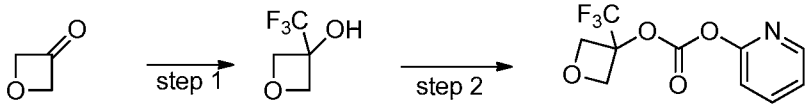
Step 2:

To a suspension of sodium hydride, 60% in mineral oil (0.817 g, 20.43 mmol) in THF (55 mL) was added 3-methyloxetan-3-ol (1.5 g, 17.03 mmol) at 0°C. After stirring 30 min, the solution was transferred to a solution of di(pyridin-2-yl) carbonate (3.68 g, 17.03 mmol) in THF (55 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. The reaction was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, concentrated to give a residue that was purified by Biotage(5-40% EtOAc:Hex) to afford the desired product 3-methyloxetan-3-yl pyridin-2-yl carbonate(1.00g, 28.1% yield) as an oil. ^{1}H NMR (400MHz, CHLOROFORM-d) d 8.52 - 8.35 (m, 1H), 7.84 (ddd, *J*=8.1, 7.3, 2.1 Hz, 1H), 7.31 - 7.27 (m, 1H), 7.15 (dt, *J*=8.1, 0.8 Hz, 1H), 4.97 - 4.85 (m, 2H), 4.54 (d, *J*=8.0 Hz, 2H), 1.86 (s, 3H).

Preparation of pyridin-2-yl (3-(trifluoromethyl)oxetan-3-yl) carbonate



Scheme:



Step 1:

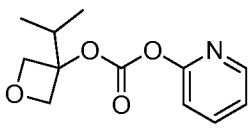
Tetrahydrofuran (110 mL) was added to a round bottom flask and placed under N_2. trimethyl(trifluoromethyl)silane (7.18 mL, 48.6 mmol) was then added

and stirred under N_2 and then cooled to 0 °C. oxetan-3-one (2.5 g, 34.7 mmol) was then added via syringe and stirred for 5 minutes at 0 °C to ensure complete mixing. TBAF (0.347 mL, 0.347 mmol) was added dropwise slowly via syringe and allowed to warm up to RT for 1 hr. The reaction was then cooled back down to 0 °C and added 30 mL of 1N HCl and stirred at RT for overnight. The reaction was then diluted with EtOAc and separated with water. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to give the product 3-(trifluoromethyl)oxetan-3-ol(2.00g, 40.6% yield) as an orange thin oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 4.82 - 4.74 (m, 2H), 4.70 - 4.60 (m, 2H), 3.23 (br. s., 1H).

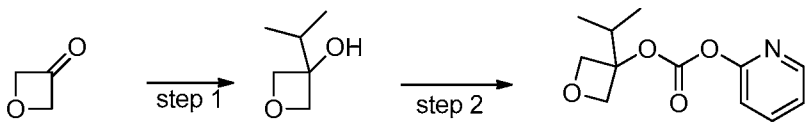
Step 2:

To a suspension of sodium hydride, 60% in mineral oil (0.676 g, 16.89 mmol) in THF (55 mL) was added 3-(trifluoromethyl)oxetan-3-ol (2 g, 14.08 mmol) at 0°C. After stirring 30 min, the solution was transferred to a solution of di(pyridin-2-yl) carbonate (3.04 g, 14.08 mmol) in THF (55 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. The reaction was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, concentrated to give a residue that was purified by Biotage(90 g column, 5-40% EtOAc:Hex) to afford the desired product pyridin-2-yl (3-(trifluoromethyl)oxetan-3-yl) carbonate(1.00g, 27% yield) as a clear oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.44 (ddd, *J*=5.0, 2.0, 0.8 Hz, 1H), 7.92 - 7.81 (m, 1H), 7.33 (ddd, *J*=7.3, 5.0, 1.0 Hz, 1H), 7.18 (dt, *J*=8.1, 0.8 Hz, 1H), 5.13 - 5.05 (m, 2H), 4.94 - 4.86 (m, 2H).

Preparation of 3-isopropyloxetan-3-yl pyridin-2-yl carbonate



Scheme:



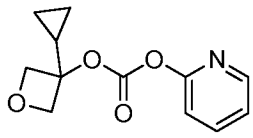
Step 1:

Isopropylmagnesium chloride(13.88 mL, 27.8 mmol) was added dropwise via syringe to a solution of oxetan-3-one (2, 27.8 mmol) in Diethyl ether (110 mL) at 0 °C and stirred at this temp for 1 hr before warming up to RT. The reaction was quenched with sat. ammonium chloride and extracted with ether. The organic layer was washed with brine, collected, dried over $MgSO_4$, filtered and partially evaporated to give the crude product 3-isopropyloxetan-3-ol(2.00g, 62% yield) as an oil. ^{1}H NMR (400MHz, CHLOROFORM-d) d 4.55 (d, *J*=7.0 Hz, 2H), 4.50 (d, *J*=7.0 Hz, 2H), 2.14 - 2.04 (m, 1H), 0.93 (s, 3H), 0.92 (s, 3H).

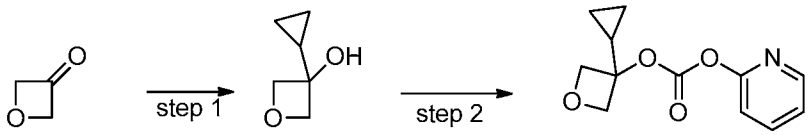
Step 2:

To a suspension of sodium hydride, 60% in mineral oil (331 mg, 8.26 mmol) in THF (25 mL) was added 3-isopropyloxetan-3-ol (800 mg, 6.89 mmol) at 0°C. After stirring 30 min, the solution was transferred to a solution of di(pyridin-2-yl) carbonate (1489 mg, 6.89 mmol) in THF (25 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. The reaction was diluted with EtOAc, washed with brine, dried over MgSO4, filtered, concentrated to give a residue that was purified by Biotage eluting with 20% EtOAc in hexanes to afford the desired product 3-isopropyloxetan-3-yl pyridin-2-yl carbonate(320mg, 20.2% yield) as an oil. ^{1}H NMR (400MHz, CHLOROFORM-d) d 8.47 - 8.39 (m, 1H), 7.86 - 7.78 (m, 1H), 7.31 - 7.24 (m, 1H), 7.15 (d, *J*=8.0 Hz, 1H), 4.89 (d, *J*=8.5 Hz, 2H), 4.67 (d, *J*=8.5 Hz, 2H), 2.53 (dt, *J*=13.7, 7.0 Hz, 1H), 1.13 (s, 3H), 1.12 (s, 3H).

Preparation of 3-cyclopropyloxetan-3-yl pyridin-2-yl carbonate



Scheme:



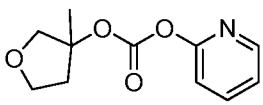
Step 1:

Cyclopropylmagnesium bromide (27.8 mL, 13.88 mmol) was added dropwise via syringe to a solution of oxetan-3-one (1 g, 13.88 mmol) in Diethyl ether (55 mL) at 0 °C and stirred at this temp for 1 hr before warming up to RT. The reaction was quenched with sat. ammonium chloride and extracted with ether. The organic layer was washed with brine, collected, dried over $MgSO_4$, filtered and evaporated to give the crude product 3-cyclopropyloxetan-3-ol(1g, 63.1% yield) as an oil. ^{1}H NMR (400MHz, CHLOROFORM-d) d 4.54 (d, *J*=7.3 Hz, 2H), 4.38 (d, *J*=7.3 Hz, 2H), 1.29 - 1.19 (m, 1H), 0.62 - 0.55 (m, 2H), 0.49 - 0.44 (m, 2H).

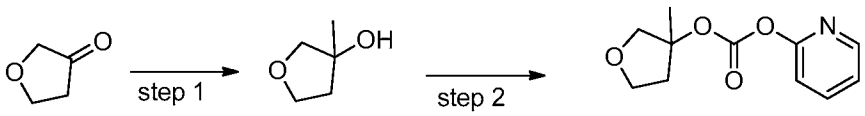
Step 2:

To a suspension of sodium hydride, 60% in mineral oil (315 mg, 7.88 mmol) in THF (20 mL) was added 3-cyclopropyloxetan-3-ol (750 mg, 6.57 mmol) at 0°C. After stirring 30 min, the solution was transferred to a solution of di(pyridin-2-yl) carbonate (1421 mg, 6.57 mmol) in THF (20 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. The reaction was diluted with EtOAc followed by brine. The organic layer was collected, dried over $MgSO_4$, filtered and evaporated to give the crude material. The crude material was purified via biotage(40 g column, 5-40% EtOAc:Hex) to give the expected product 3-cyclopropyloxetan-3-yl pyridin-2-yl carbonate(290mg, 18.76% yield) as a clear thick oil. ^{1}H NMR (400MHz, CHLOROFORM-d) d 8.54 - 8.36 (m, 1H), 7.89 - 7.77 (m, 1H), 7.34 - 7.25 (m, 1H), 7.17 (d, *J*=8.3 Hz, 1H), 4.84 (d, *J*=8.5 Hz, 2H), 4.42 (d, *J*=8.3 Hz, 2H), 1.67 - 1.56 (m, 1H), 0.81 - 0.72 (m, 2H), 0.72 - 0.63 (m, 2H).

Preparation of 3-methyltetrahydrofuran-3-yl pyridin-2-yl carbonate



Scheme:



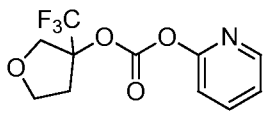
Step 1:

Methylmagnesium bromide (4.26 mL, 12.78 mmol) was added dropwise via syringe to a solution of dihydrofuran-3(2H)-one (1 g, 11.62 mmol) in Diethyl ether (55 mL) at 0 °C and stirred at this temp for 1 hr before warming up to RT. The reaction was quenched with sat. ammonium chloride and extracted with ether. The organic layer was washed with brine, collected, dried over $MgSO_4$, filtered and evaporated to give the crude product 3-methyltetrahydrofuran-3-ol(394mg, 33.2% yield) as a clear oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 4.05 (td, *J*=8.5, 7.4 Hz, 1H), 3.91 (td, *J*=8.5, 4.5 Hz, 1H), 3.71 (dd, *J*=9.2, 0.9 Hz, 1H), 3.53 (d, *J*=9.3 Hz, 1H), 2.00 - 1.95 (m, 2H), 1.43 (s, 3H).

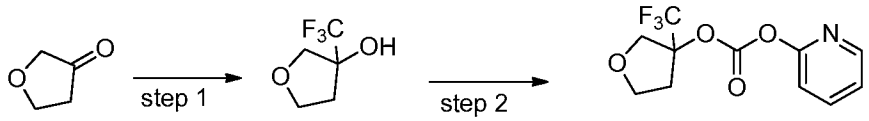
Step 2:

To a suspension of sodium hydride, 60% in mineral oil (185 mg, 4.63 mmol) in THF (20 mL) was added 3-methyltetrahydrofuran-3-ol (394 mg, 3.86 mmol) at 0°C. After stirring 30 min, the solution was transferred to a solution of di(pyridin-2-yl) carbonate (834 mg, 3.86 mmol) in THF (20 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. The reaction was diluted with EtOAc, washed with brine, dried over MgSO4, filtered, concentrated to give a residue that was purified by Biotage(5-40% EtOAc:Hex) to afford the desired product 3-methyltetrahydrofuran-3-yl pyridin-2-yl carbonate(334mg, 38.8% yield) as an oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.48 - 8.29 (m, 1H), 7.91 - 7.73 (m, 1H), 7.29 - 7.25 (m, 1H), 7.16 - 7.12 (m, 1H), 4.23 (d, *J*=10.3 Hz, 1H), 4.02 (td, *J*=8.5, 7.2 Hz, 1H), 3.95 (td, *J*=8.4, 4.5 Hz, 1H), 3.76 (d, *J*=10.3 Hz, 1H), 2.58 - 2.47 (m, 1H), 2.11 - 2.02 (m, 1H), 1.76 (s, 3H).

Preparation of pyridin-2-yl (3-(trifluoromethyl)tetrahydrofuran-3-yl) carbonate



Scheme:



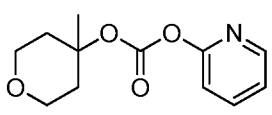
Step 1:

Tetrahydrofuran (55 mL) was added to a round bottom flask and placed under N_2. trimethyl(trifluoromethyl)silane (2.404 mL, 16.26 mmol) was then added and stirred under N_2 and then cooled to 0 °C. Dihydrofuran-3(2H)-one (1 g, 11.62 mmol) was then added via syringe and stirred for 5 minutes at 0 °C to ensure complete mixing. TBAF (0.116 mL, 0.116 mmol) was added dropwise slowly via syringe and allowed to warm up to RT for 1 hr. The reaction was then cooled back down to 0 °C and added 30 mL of 1N HCl and stirred at RT for overnight. The reaction was then diluted with EtOAc and separated with water. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to give the product 3-(trifluoromethyl)tetrahydrofuran-3-ol(800mg, 44.1% yield) as an orange thin oil. ^1H NMR (400MHz, CHLOROFORM-d) d 4.05 - 3.92 (m, 3H), 3.80 - 3.75 (m, 1H), 2.31 (dt, *J*=13.3, 8.4 Hz, 1H), 2.08 - 2.03 (m, 1H).

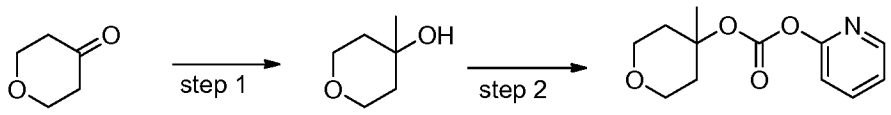
Step 2:

To a suspension of sodium hydride, 60% in mineral oil (246 mg, 6.15 mmol) in THF (25 mL) was added 3-(trifluoromethyl)tetrahydrofuran-3-ol (800 mg, 5.12 mmol) at 0ºC. After stirring 30 min, the solution was transferred to a solution of di(pyridin-2-yl) carbonate (1108 mg, 5.12 mmol) in THF (25 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. The reaction was diluted with EtOAc, washed with brine, dried over MgSO4, filtered, concentrated to give a residue that was purified by Biotage(5-40% EtOAc:Hex) to afford the desired product pyridin-2-yl (3-(trifluoromethyl)tetrahydrofuran-3-yl) carbonate(339mg, 23.86% yield) as an oil. ^1H NMR (400MHz, CHLOROFORM-d) δ 8.47 - 8.33 (m, 1H), 7.88 - 7.82 (m, 1H), 7.30 (ddd, *J*=7.4, 4.9, 1.0 Hz, 1H), 7.16 (d, *J*=8.3 Hz, 1H), 4.40 - 4.21 (m, 2H), 4.11 - 3.91 (m, 2H), 2.71 - 2.61 (m, 1H), 2.58 - 2.46 (m, 1H).

Preparation of 4-methyltetrahydro-2H-pyran-4-yl pyridin-2-yl carbonate



Scheme:



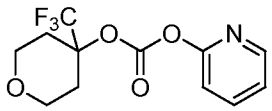
Step 1:

Methylmagnesium bromide (3.66 mL, 10.99 mmol) was added dropwise via syringe to a solution of dihydro-2H-pyran-4(3H)-one (1 g, 9.99 mmol) in Diethyl ether (50 mL) at 0 °C and stirred at this temp for 1 hr before warming up to RT. The reaction was quenched with sat. ammonium chloride and extracted with ether. The organic layer was washed with brine, collected, dried over $MgSO_4$, filtered and evaporated to give the crude product 4-methyltetrahydro-2H-pyran-4-ol(1g, 86% yield) as an oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 3.82 - 3.73 (m, 2H), 3.73 - 3.66 (m, 2H), 1.74 - 1.64 (m, 3H), 1.54 (ddt, *J*=13.7, 4.6, 2.1 Hz, 2H), 1.41 (br. s, 1H), 1.28 (s, 3H).

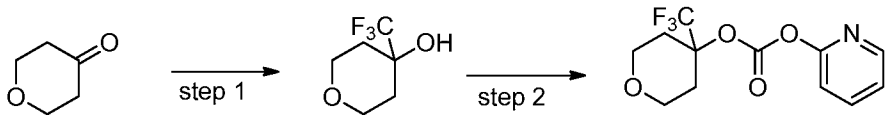
Step 2:

To a suspension of sodium hydride, 60% in mineral oil (207 mg, 5.17 mmol) in THF (20 mL) was added 4-methyltetrahydro-2H-pyran-4-ol (500 mg, 4.30 mmol) at 0°C. After stirring 30 min, the solution was transferred to a solution of di(pyridin-2-yl) carbonate (931 mg, 4.30 mmol) in THF (20 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. At room temperature, to the reaction mixture was added sat. aq. NH_4Cl (1 mL) upon which brief and significant effervescence was observed. The mixture was transferred to a 250 mL separatory funnel and was diluted with Et2O (50 mL). The solution was washed with water:brine (25 mL: 25 mL). The aq. phase was extracted with EtOAc (100 mL). The combined organics were dried over MgSO4; filtered; then concentrated in vacuo. The resulting residue was dissolved in acetone and then concentrated onto Celite in vacuo. The resulting powder was subjected to SiO2 purification on the Biotage system [90g SiO_2 column, hexanes:EtOAc 90:10 to 60:40 over 8 CV] to get the product as a clear oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.48 - 8.39 (m, 1H), 7.87 - 7.76 (m, 1H), 7.30 - 7.24 (m, 2H), 7.16 - 7.09 (m, 1H), 3.83 - 3.69 (m, 4H), 2.29 - 2.16 (m, 2H), 1.80 (ddd, *J*=14.3, 8.9, 5.9 Hz, 2H), 1.66 (s, 3H).

Preparation of pyridin-2-yl (4-(trifluoromethyl)tetrahydro-2H-pyran-4-yl) carbonate



Scheme:



Step 1:

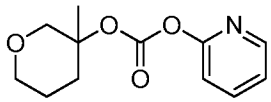
Tetrahydrofuran (110 mL) was added to a round bottom flask and placed under N_2. trimethyl(trifluoromethyl)silane (4.13 mL, 28.0 mmol) was then added and stirred under N_2 and then cooled to 0 °C. Dihydro-2H-pyran-4(3H)-one (1.845 mL, 19.98 mmol) was then added via syringe and stirred for 5 minutes at 0 °C to ensure complete mixing. TBAF (0.200 mL, 0.200 mmol) was added dropwise slowly via syringe. The reaction was then allowed to warm up to RT for 30 min. The reaction was then cooled back down to 0 °C and added 1M HCl (50 mL) and then stirred at RT for overnight. The reaction was diluted with EtOAc and separated with brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to give the crude material which was crystallized from hexane to give the product 4-(trifluoromethyl)tetrahydro-2H-pyran-4-ol (1.45 g, 8.52 mmol, 42.7 % yield) as white crystals. ^{1}H NMR (400MHz, CHLOROFORM-d) d 3.96 - 3.84 (m, 2H), 3.76 (td, *J*=12.1, 2.1 Hz, 2H), 2.08 - 1.90 (m, 3H), 1.65 - 1.48 (m, 2H).

Step 2:

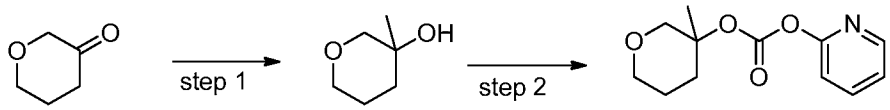
To a suspension of sodium hydride, 60% in mineral oil (226 mg, 5.64 mmol) in THF (20 mL) was added 4-(trifluoromethyl)tetrahydro-2H-pyran-4-ol (800 mg, 4.70 mmol) in 5 mL of THF via syringe at 0°C. After stirring 30 min, the solution was transferred to a solution of di(pyridin-2-yl) carbonate (1017 mg, 4.70 mmol) in THF (20 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. After 2 hr the reaction was diluted with EtOAc and washed with brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to give the crude material. The crude material was purified via biotage (90 g column, 5-40% EtOAc:Hex) to give pyridin-2-yl (4-

(trifluoromethyl)tetrahydro-2H-pyran-4-yl) carbonate (500 mg, 1.717 mmol, 36.5 % yield) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.47 - 8.36 (m, 1H), 7.90 - 7.77 (m, 1H), 7.37 - 7.25 (m, 1H), 7.23 - 7.06 (m, 1H), 3.98 (dd, *J*=11.7, 4.4 Hz, 2H), 3.85 - 3.68 (m, 2H), 2.53 (dd, *J*=14.2, 2.1 Hz, 2H), 2.11 - 2.00 (m, 2H).

Preparation of 3-methyltetrahydro-2H-pyran-3-yl pyridin-2-yl carbonate



Scheme:



Step 1:

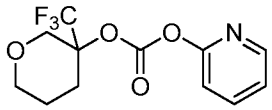
Methylmaganesium bromide(1.831 mL, 5.49 mmol) was added dropwise via syringe to a solution of dihydro-2H-pyran-3(4H)-one (500 mg, 4.99 mmol) in Diethyl ether (50 mL) at -20 °C and stirred at this temp for 1 hr before warming up to RT. The reaction was quenched with sat. ammonium chloride and extracted with ether. The organic layer was washed with brine, collected, dried over $MgSO_4$, filtered and partially evaporated to give the crude product 3-methyltetrahydro-2H-pyran-3-ol(480mg, 83% yield) as an oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 3.90 - 3.81 (m, 1H), 3.55 - 3.50 (m, 1H), 3.40 (td, *J*=11.3, 2.8 Hz, 1H), 3.31 (d, *J*=11.3 Hz, 1H), 2.16 (br. s., 1H), 1.94 - 1.81 (m, 1H), 1.78 - 1.69 (m, 1H), 1.59 - 1.47 (m, 2H), 1.18 - 1.11 (m, 3H).

Step 2:

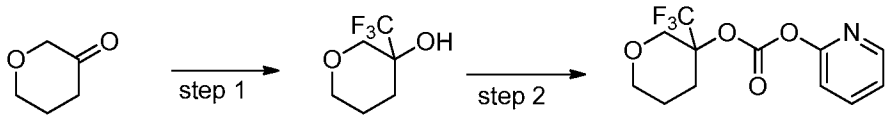
To a suspension of sodium hydride, 60% in mineral oil (207 mg, 5.17 mmol) in THF (20 mL) was added 3-methyltetrahydro-2H-pyran-3-ol (500 mg, 4.30 mmol) at 0°C. After stirring 30 min, the solution was transferred to a solution of di(pyridin-2-yl) carbonate (931 mg, 4.30 mmol) in THF (20 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. The reaction was diluted with EtOAc followed by brine. The organic layer was collected, dried over $MgSO_4$, filtered and evaporated to give the crude material. the crude material was purified via biotage(40 g column, 5-40% EtOAc:Hex) to give the

expected product 3-methyltetrahydro-2H-pyran-3-yl pyridin-2-yl carbonate(173mg, 17.94% yield) as a clear thick oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.50 - 8.30 (m, 1H), 7.89 - 7.74 (m, 1H), 7.27 - 7.22 (m, 1H), 7.14 (d, *J*=8.3 Hz, 1H), 4.22 - 4.05 (m, 1H), 3.88 - 3.74 (m, 1H), 3.60 - 3.49 (m, 1H), 3.44 (d, *J*=12.0 Hz, 1H), 2.38 - 2.20 (m, 1H), 2.03 - 1.88 (m, 1H), 1.84 - 1.72 (m, 1H), 1.63 - 1.57 (m, 1H), 1.56 (s, 3H).

Preparation of pyridin-2-yl (3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl) carbonate



Scheme:



Step 1:

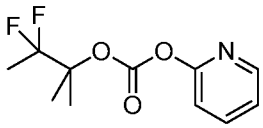
Tetrahydrofuran (50 mL) was added to a round bottom flask and placed under N_2. trimethyl(trifluoromethyl)silane (1.033 mL, 6.99 mmol) was then added and stirred under N_2 and then cooled to 0 °C. Dihydro-2H-pyran-3(4H)-one (500 mg, 4.99 mmol) was then added via syringe and stirred for 5 minutes at 0 °C to ensure complete mixing. TBAF (0.050 mL, 0.050 mmol) was added dropwise slowly via syringe. The reaction was then allowed to warm up to RT for 30 min. The reaction was then cooled back down to 0 °C and added 1M HCl (50 mL) and then stirred at RT for overnight. The reaction was diluted with water and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to give the crude product 3-(trifluoromethyl)tetrahydro-2H-pyran-3-ol(400mg, 47.1% yield) as an oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 4.01 - 3.93 (m, 1H), 3.82 (dd, *J*=11.8, 2.5 Hz, 1H), 3.60 (d, *J*=12.0 Hz, 1H), 3.41 (td, *J*=11.8, 2.5 Hz, 1H), 2.10 - 2.08 (m, 2H), 1.97 - 1.90 (m, 1H), 1.82 (dd, *J*=12.9, 4.4 Hz, 1H), 1.65 - 1.55 (m, 1H).

Step 2:

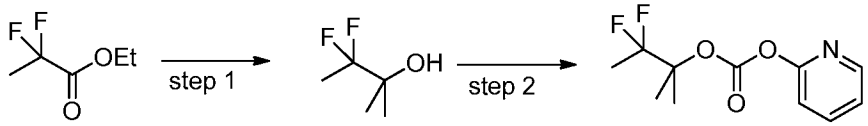
To a suspension of sodium hydride, 60% in mineral oil (141 mg, 3.53 mmol) in THF (20 mL) was added 3-(trifluoromethyl)tetrahydro-2H-pyran-3-ol (500 mg, 2.94 mmol) at 0°C. After stirring 30 min, the solution was transferred to a solution of

di(pyridin-2-yl) carbonate (635 mg, 2.94 mmol) in THF (20 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. The reaction was diluted with EtOAc followed by brine. The organic layer was collected, dried over $MgSO_4$, filtered and evaporated to give the crude material. The crude material was purified via biotage(40 g column, 5-40% EtOAc:Hex) to give the expected product pyridin-2-yl (3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl) carbonate(195mg, 22.78% yield) as a clear thick oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.43 (dd, *J*=4.9, 1.4 Hz, 1H), 7.88 - 7.75 (m, 1H), 7.32 - 7.24 (m, 1H), 7.19 (d, *J*=8.3 Hz, 1H), 4.70 (dd, *J*=12.4, 2.6 Hz, 1H), 4.02 - 3.92 (m, 1H), 3.67 (d, *J*=12.3 Hz, 1H), 3.60 - 3.42 (m, 1H), 2.68 - 2.53 (m, 1H), 2.08 - 1.92 (m, 2H), 1.77 - 1.62 (m, 1H).

Preparation of 3,3-difluoro-2-methylbutan-2-yl pyridin-2-yl carbonate



Scheme:



Step 1:

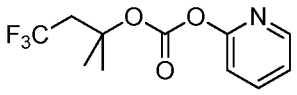
Methylmagnesium bromide(24.91 mL, 74.7 mmol) was added dropwise via syringe to a solution of ethyl 2,2-difluoropropanoate (3.44 g, 24.91 mmol) in Diethyl ether (50 mL) at -20 °C and stirred at this temp for 1 hr before warming up to RT. The reaction was quenched with sat. ammonium chloride and extracted with ether. The organic layer was washed with brine, collected, dried over $MgSO_4$, filtered and partially evaporated to give the crude product 3,3-difluoro-2-methylbutan-2-ol(1.84g, 59.5% yield) as an oil. ^{1}H NMR (500MHz, CHLOROFORM-d) d 1.68 - 1.58 (m, 3H), 1.31 (t, *J*=1.2 Hz, 6H).

Step 2:

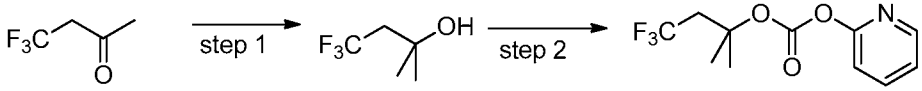
To a suspension of sodium hydride, 60% in mineral oil (0.652 g, 16.31 mmol) in THF (25 mL) was added 3,3-difluoro-2-methylbutan-2-ol (1.84 g, 14.82 mmol) at 0°C. After stirring 30 min, the solution was transferred to a solution of di(pyridin-2-

yl) carbonate (3.20 g, 14.82 mmol) in THF (25 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. The reaction was diluted with EtOAc, washed with brine, dried over MgSO4, filtered, concentrated to give a residue that was purified by Biotage eluting with 10-50% EtOAc in hexanes to afford the desired product 3,3-difluoro-2-methylbutan-2-yl pyridin-2-yl carbonate(500mg, 13.76%) as an oil that later crystallized to a white solid upon standing. ^{1}H NMR (500MHz, CHLOROFORM-d) δ 8.43 (ddd, *J*=4.9, 2.0, 0.7 Hz, 1H), 7.95 - 7.75 (m, 1H), 7.31 - 7.24 (m, 1H), 7.15 (dt, *J*=8.2, 0.8 Hz, 1H), 1.72 (s, 6H), 1.77 - 1.66 (m, 3H).

Preparation of pyridin-2-yl (4,4,4-trifluoro-2-methylbutan-2-yl) carbonate



Scheme:



Step 1:

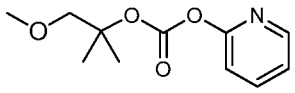
Methylmaganesium bromide (1.454 mL, 4.36 mmol) was added dropwise via syringe to a solution of 4,4,4-trifluorobutan-2-one (500 mg, 3.97 mmol) in Diethyl ether (25 mL) at 0 °C and stirred at this temp for 1 hr before warming up to RT. The reaction was quenched with sat. ammonium chloride and extracted with ether. The organic layer was washed with brine, collected, dried over MgSO4, filtered and partially evaporated to give the crude product 4,4,4-trifluoro-2-methylbutan-2-ol(500mg, 89% yield) as an oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 2.34 (q, *J*=11.5 Hz, 2H), 1.88 (br. s, 1H), 1.37 (d, *J*=0.8 Hz, 6H).

Step 2:

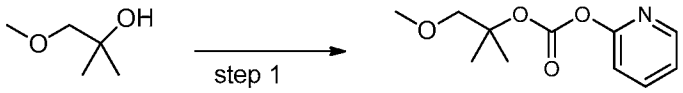
To a suspension of sodium hydride, 60% in mineral oil (169 mg, 4.22 mmol) in THF (20 mL) was added 4,4,4-trifluoro-2-methylbutan-2-ol (500 mg, 3.52 mmol) at 0°C. After stirring 30 min, the solution was transferred to a solution of di(pyridin-2-yl) carbonate (761 mg, 3.52 mmol) in THF (20 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. The reaction was diluted with EtOAc followed by brine. The organic layer was

collected, dried over $MgSO_4$, filtered and evaporated to give the crude material. The crude material was purified via biotage(40 g column, 5-40% EtOAc:Hex) to give the expected product pyridin-2-yl (4,4,4-trifluoro-2-methylbutan-2-yl) carbonate(150mg, 16.2% yield) as a clear thick oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.43 (dd, *J*=4.9, 1.4 Hz, 1H), 7.91 - 7.76 (m, 1H), 7.30 - 7.24 (m, 1H), 7.11 (d, *J*=8.3 Hz, 1H), 2.83 (q, *J*=11.0 Hz, 2H), 1.75 - 1.61 (m, 6H).

Preparation of 1-methoxy-2-methylpropan-2-yl pyridin-2-yl carbonate



Scheme:

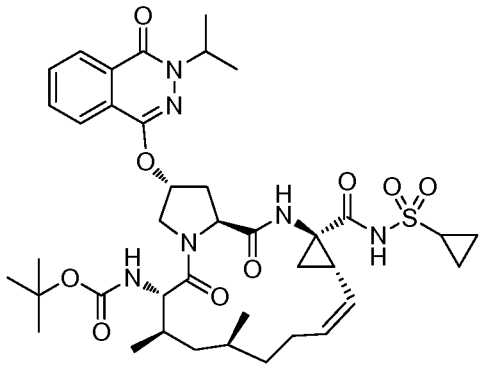


Step 1:

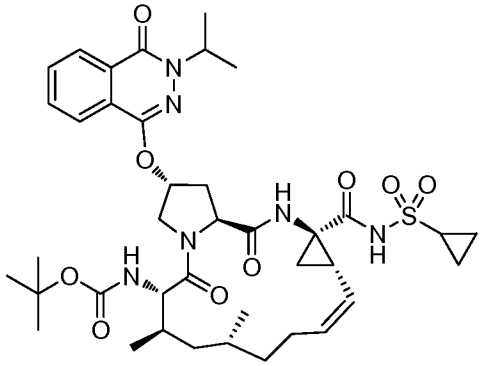
To a 40 mL vial equipped with a stir bar was added 1-methoxy-2-methylpropan-2-ol (361 mg, 3.47 mmol) and THF (15 mL). To the solution was added sodium hydride, 60% in mineral oil (167 mg, 4.16 mmol) upon which vigorous effervescence was observed. The mixture was placed under a stream of N2 until the effervescence decreased significantly (app. 5 mins). The vial was then capped with a septum-screw cap and the solution was stirred at room temperature for 30 minutes. To the slightly turbid mixture was added 1-methoxy-2-methylpropan-2-yl pyridin-2-yl carbonate (241 mg, 1.070 mmol, 30.8 % yield) upon which minor and brief effervescence was observed. The solution was stirred at room temperature for 65h, TLC found two well resolved spots. To the mixture was added a spatula tip of NH_4Cl, then the mixture was concentrated in vacuo. The residue was diluted with acetone and then concentrated onto Celite in vacuo. The resulting powder was subjected to SiO2 chromatography on the Biotage system as indicated (see attached. hexanes:EtOAc; 5% EtOAc to 50% EtOAc). This purification afforded the desired product 1-methoxy-2-methylpropan-2-yl pyridin-2-yl carbonate(241mg, 30.8% yield) as a clear oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.42 (ddd, *J*=5.0, 2.0, 0.8

Hz, 1H), 7.86 - 7.72 (m, 1H), 7.24 (ddd, *J*=7.4, 4.9, 0.8 Hz, 1H), 7.12 (dt, *J*=8.1, 0.8 Hz, 1H), 3.57 (s, 2H), 3.44 (s, 3H), 1.68 - 1.48 (m, 6H).

Preparation of 1001 and 1002



Compound 1001



Compound 1002

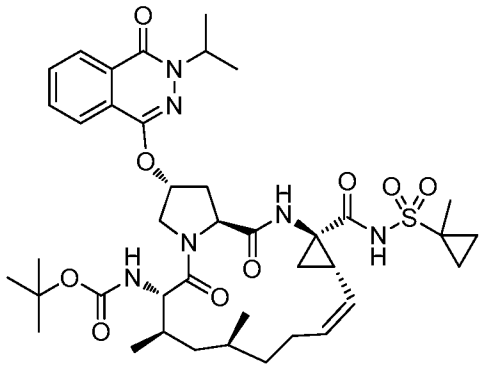
Compounds 1001 and 1002 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1001: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-isopropyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 783.5 (M^++1).

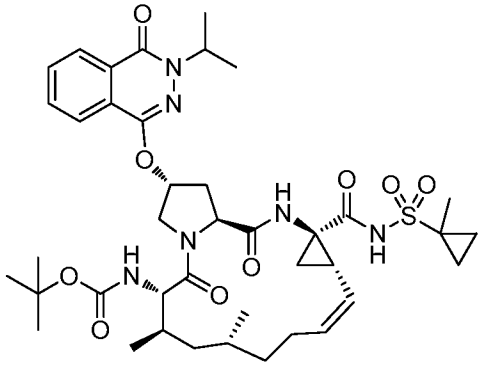
Compound 1002: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-isopropyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 9.01 (br. s., 1H), 8.25 (d, J=5.2 Hz, 1H), 7.88 (d, J=5.5 Hz, 4H), 7.14 (br. s., 1H), 5.55 (br. s., 3H), 5.23 - 5.18 (m, 1H), 5.01 (br. s., 1H), 4.74 (br. s., 1H), 4.48 (br. s., 1H), 3.91 - 3.86 (m, 1H), 3.68 (t, J=8.9 Hz, 1H), 2.64 (br. s., 1H), 2.60 (br. s., 1H), 2.29 (d, J=10.7 Hz, 2H), 1.91 (br. s., 1H), 1.80 (br. s., 1H), 1.61 (br. s., 2H), 1.53 (br. s., 1H), 1.42 (br. s., 2H), 1.37 - 1.32 (m, 6H), 1.24

(br. s., 1H), 1.15 (br. s., 2H), 1.06 (d, J=11.9 Hz, 2H), 1.01 (s, 9H), 0.92 (d, J=6.7 Hz, 3H), 0.86 (d, J=6.4 Hz, 3H), 0.70 (br. s., 1H). MS: MS *m/z* 783.5 (M^++1).

Preparation of Compound 1003 and 1004



Compound 1003



Compound 1004

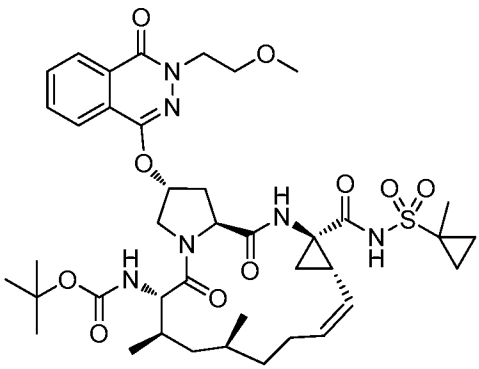
Compounds 1003 and 1004 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1003: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 797.5 (M^++1).

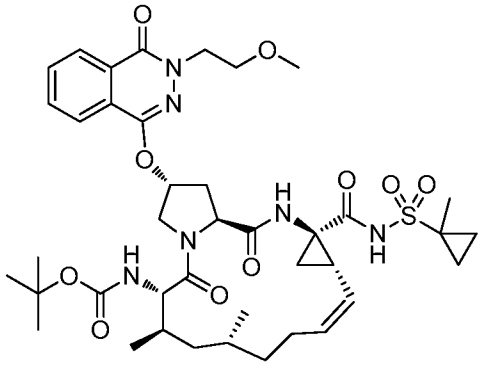
Compound 1004: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 8.23 (d, J=5.5 Hz, 1H), 7.92 - 7.84 (m, 4H), 7.09 (d, J=7.0 Hz, 1H), 5.55 (br. s., 2H), 5.22 - 5.16 (m, 1H), 4.94 (br. s., 1H), 4.73 (br. s., 1H), 4.49 (br. s., 1H), 3.91 - 3.87 (m, 1H), 3.67 (t, J=9.5 Hz, 1H), 2.60 (br. s., 2H), 2.28 (br. s., 2H), 1.90 (s, 1H), 1.80 (br. s., 1H), 1.62 (br. s., 2H), 1.49 (br. s., 1H), 1.39 (br. s., 3H), 1.33 (t, J=5.8 Hz, 8H),

1.24 (d, J=16.2 Hz, 2H), 1.17 - 1.01 (m, 4H), 0.98 (s, 9H), 0.91 (d, J=6.7 Hz, 3H), 0.85 (d, J=6.1 Hz, 3H), 0.70 (br. s., 1H). MS: MS *m/z* 797.5 (M^++1).

Preparation of Compound 1005 and 1006



Compound 1005



Compound 1006

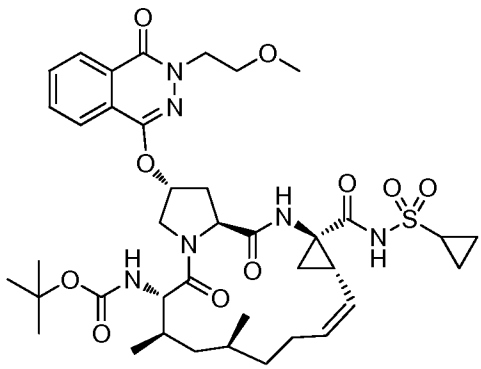
Compounds 1005 and 1006 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1005: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(2-methoxyethyl)-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 813.5 (M^++1).

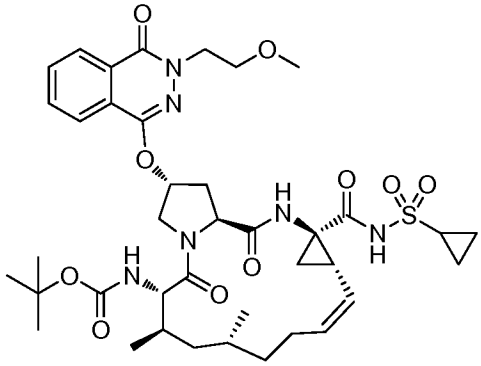
Compound 1006: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(2-methoxyethyl)-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 9.15 (br. s., 1H), 8.24 (d, J=6.7 Hz, 1H), 7.96 - 7.85 (m, 4H), 7.15 (br. s., 1H), 5.53 (br. s., 2H), 4.95 (br. s., 1H), 4.70 (br. s., 1H), 4.47 (br. s., 1H), 4.27 - 4.16 (m, 2H), 3.91 - 3.85 (m, 1H), 3.78 - 3.66 (m, 4H), 3.43 (d, J=5.8 Hz, 3H), 2.64 (br. s., 2H), 2.35 - 2.24 (m, 2H), 1.90 (d, J=15.0 Hz, 1H), 1.79 (br. s., 1H), 1.67 (br. s., 1H), 1.61

(br. s., 1H), 1.50 (br. s., 2H), 1.39 (br. s., 3H), 1.26 (br. s., 2H), 1.14 (s, 2H), 1.07 (s, 9H), 0.92 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.1 Hz, 3H), 0.72 (br. s., 1H). MS: MS *m/z* 813.5 (M^++1).

Preparation of Compound 1007 and 1008



Compound 1007



Compound 1008

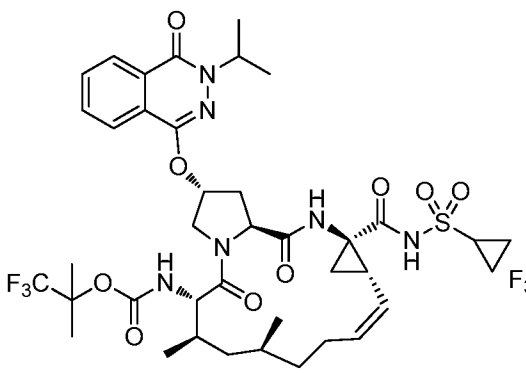
Compounds 1007 and 1008 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1007: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(2-methoxyethyl)-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 799.5 (M^++1).

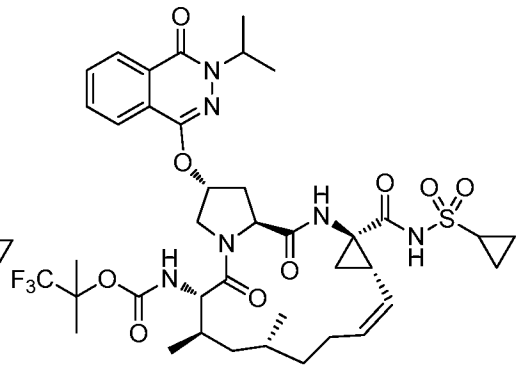
Compound 1008: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(2-methoxyethyl)-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 9.02 (br. s., 1H), 8.24 (d, J=6.1 Hz, 1H), 7.89 (d, J=9.2 Hz, 3H), 7.14 (br. s., 1H), 5.52 (br. s., 2H), 5.03 (br. s., 1H), 4.69 (d, J=9.8 Hz, 1H), 4.44 (br. s., 1H), 4.21 (br. s., 2H), 3.85 (d, J=11.3 Hz, 1H), 3.78 - 3.65 (m, 3H), 3.26 (d, J=3.7 Hz, 3H), 2.89 (br. s.,

1H), 2.62 (br. s., 2H), 2.27 (d, J=10.1 Hz, 2H), 1.88 (br. s., 1H), 1.79 (br. s., 1H), 1.67 (br. s., 1H), 1.59 (br. s., 1H), 1.52 (br. s., 1H), 1.41 (br. s., 1H), 1.35 (br. s., 2H), 1.23 (br. s., 1H), 1.13 (br. s., 2H), 1.08 - 1.05 (m, 9H), 1.01 - 0.96 (m, 1H), 0.94 - 0.90 (m, 3H), 0.88 - 0.85 (m, 3H), 0.72 (d, J=12.2 Hz, 1H). MS: MS *m/z* 799.5 (M^++1).

Preparation of Compound 1009 and 1010



Compound 1009



Compound 1010

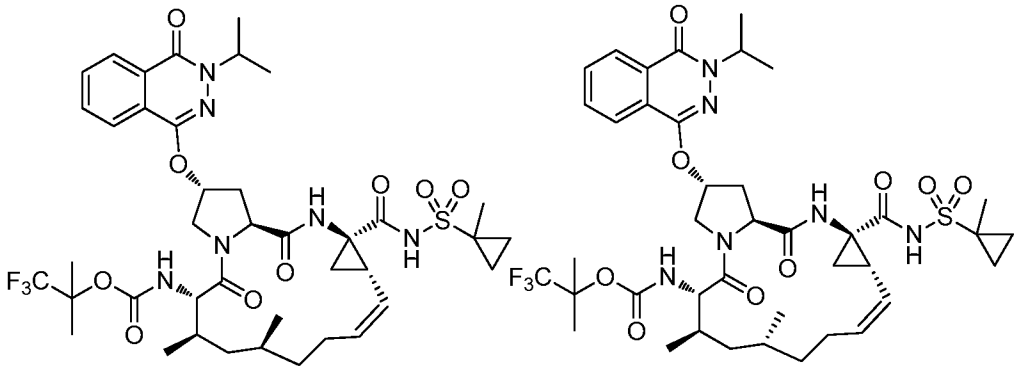
Compounds 1009 and 1010 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1009: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-isopropyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 837.5 (M^++1).

Compound 1010: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-isopropyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.22 (br. s., 1H), 9.04 (br. s., 1H), 8.30 - 8.25 (m, 1H), 7.97 - 7.86 (m, 3H), 7.83 (d, J=7.9 Hz, 1H), 5.57 (br. s., 1H), 5.52 (br. s., 1H), 5.23 (quin, J=6.6 Hz, 1H), 5.06 (br. s., 1H), 4.68 (d, J=11.0 Hz, 1H), 4.51 (t, J=8.1 Hz, 1H), 3.93 - 3.85 (m, 1H), 3.68 (dd,

J=10.7, 8.2 Hz, 1H), 2.90 (s, 1H), 2.70 - 2.58 (m, 2H), 2.38 - 2.22 (m, 2H), 1.96 - 1.88 (m, 1H), 1.88 - 1.80 (m, 1H), 1.69 (br. s., 1H), 1.61 (br. s., 1H), 1.53 (d, J=19.8 Hz, 1H), 1.43 (br. s., 1H), 1.38 - 1.32 (m, 10H), 1.32 - 1.20 (m, 1H), 1.14 (br. s., 3H), 1.02 - 0.97 (m, 1H), 0.93 (s, 1H), 0.91 (s, 3H), 0.88 (d, J=6.4 Hz, 3H), 0.74 (t, J=12.1 Hz, 1H). MS: MS *m/z* 837.5 (M^++1).

Preparation of compound 1011 and 1012



Compound 1011 Compound 1012

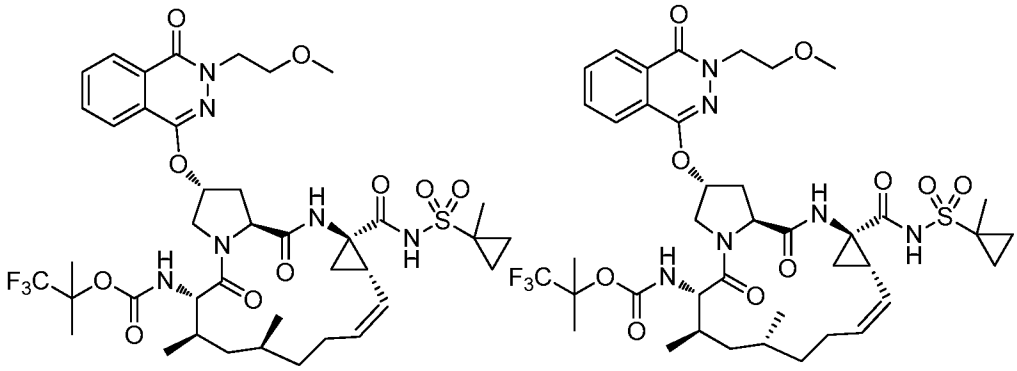
Compounds 1011 and 1012 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1011: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 851.5 (M^++1).

Compound 1012: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.07 (br. s., 1H), 9.18 (br. s., 1H), 8.30 - 8.26 (m, 1H), 7.92 - 7.88 (m, 4H), 7.84 (d, J=7.3 Hz, 1H), 5.59 - 5.50 (m, 2H), 5.23 (quin, J=6.6 Hz, 1H), 4.97 (br. s., 1H), 4.69

(br. s., 1H), 4.54 (br. s., 1H), 3.94 - 3.89 (m, 2H), 3.68 (dd, J=10.7, 8.2 Hz, 1H), 2.65 (br. s., 2H), 2.36 - 2.27 (m, 2H), 1.92 (s, 1H), 1.85 (d, J=7.6 Hz, 1H), 1.64 (br. s., 2H), 1.52 (br. s., 1H), 1.49 - 1.44 (m, 1H), 1.41 (br. s., 3H), 1.37 - 1.32 (m, 12H), 1.30 - 1.23 (m, 1H), 1.15 (br. s., 1H), 0.93 (d, J=7.0 Hz, 3H), 0.92 - 0.90 (m, 2H), 0.88 (br. s., 3H), 0.76 (br. s., 1H). MS: MS *m/z* 851.5 (M^++1).

Preparation of Compound 1013 and 1014



Compound 1013 Compound 1014

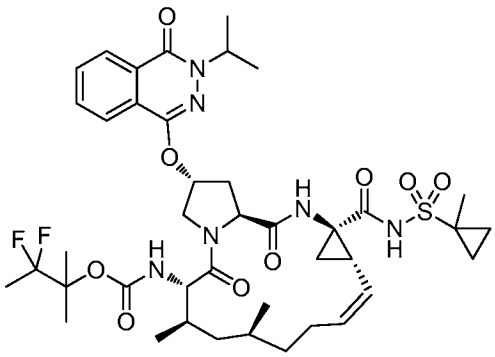
Compounds 1013 and 1014 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1013: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(2-methoxyethyl)-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 813.5 (M^++1).

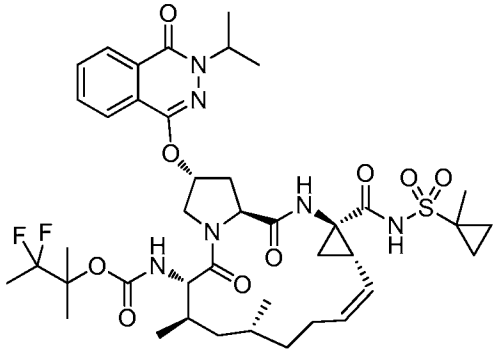
Compound 1014: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(2-methoxyethyl)-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift

11.04 (br. s., 1H), 9.18 (br. s., 1H), 8.29 - 8.25 (m, 1H), 7.94 - 7.88 (m, 3H), 7.85 (d, J=7.6 Hz, 1H), 5.54 (br. s., 2H), 4.98 (br. s., 1H), 4.67 (d, J=12.2 Hz, 1H), 4.51 (t, J=8.1 Hz, 1H), 4.29 - 4.19 (m, 2H), 3.88 (dd, J=11.6, 3.1 Hz, 1H), 3.74 (td, J=5.6, 1.8 Hz, 2H), 3.72 - 3.65 (m, 1H), 3.27 (s, 3H), 2.65 (br. s., 2H), 2.39 - 2.26 (m, 2H), 1.93 - 1.79 (m, 2H), 1.69 (br. s., 1H), 1.62 (br. s., 1H), 1.53 (br. s., 2H), 1.49 - 1.45 (m, 1H), 1.41 (s, 3H), 1.35 (br. s., 1H), 1.33 (s, 3H), 1.29 (br. s., 3H), 1.16 (br. s., 1H), 1.00 (s, 3H), 0.93 (d, J=6.7 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.76 (t, J=12.2 Hz, 1H). MS: MS *m/z* 813.5 (M^++1).

Preparation of Compound 1015 and 1016



Compound 1015



Compound 1016

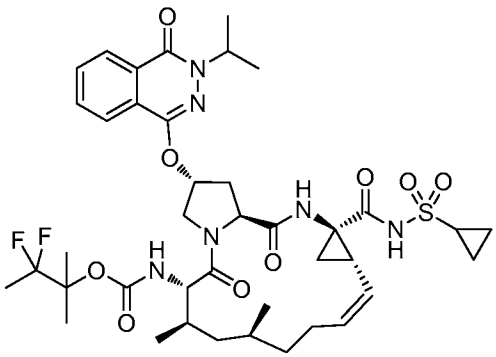
Compounds 1015 and 1016 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1015: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 847.47 (M^++1).

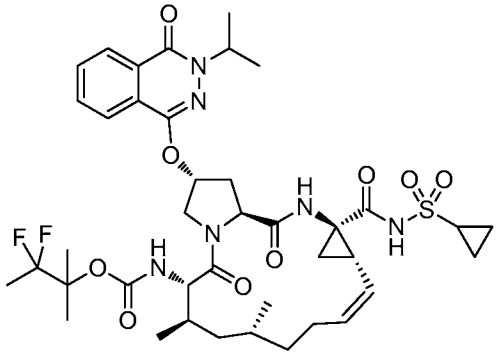
Compound 1016: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-

a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.08 (br. s., 1H), 9.16 (br. s., 1H), 8.27 (dd, J=6.3, 3.2 Hz, 1H), 7.93 - 7.86 (m, 3H), 7.61 (d, J=8.2 Hz, 1H), 5.60 - 5.50 (m, 2H), 5.23 (quin, J=6.6 Hz, 1H), 4.97 (br. s., 1H), 4.72 (d, J=11.9 Hz, 1H), 4.54 (t, J=8.2 Hz, 1H), 3.95 - 3.91 (m, 1H), 3.69 (dd, J=10.7, 8.5 Hz, 1H), 2.75 - 2.68 (m, 1H), 2.68 - 2.61 (m, 1H), 2.38 - 2.28 (m, 2H), 1.96 - 1.88 (m, 1H), 1.83 (d, J=6.4 Hz, 1H), 1.65 (br. s., 2H), 1.59 - 1.48 (m, J=19.7, 19.7 Hz, 4H), 1.47 - 1.44 (m, 2H), 1.42 (s, 3H), 1.39 - 1.38 (m, 1H), 1.35 (d, J=6.4 Hz, 6H), 1.29 (d, J=9.8 Hz, 1H), 1.23 (s, 3H), 1.14 (d, J=11.9 Hz, 1H), 0.94 (d, J=7.0 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H), 0.79 (br. s., 3H), 0.78 - 0.72 (m, 1H). MS: MS *m/z* 847.47 (M^++1).

Preparation of Compound 1017 and 1018



Compound 1017



Compound 1018

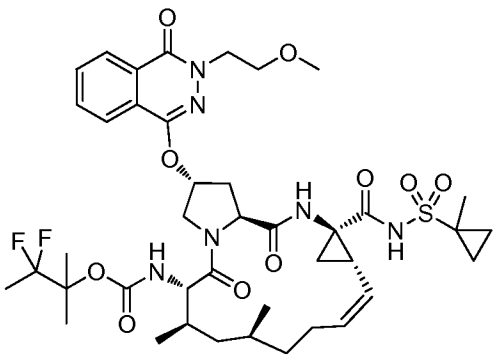
Compounds 1017 and 1018 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1017: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-isopropyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 833.46 (M^++1).

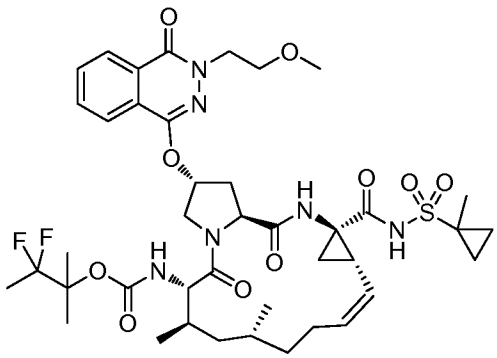
Compound 1018: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-

isopropyl-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.23 (br. s., 1H), 9.03 (br. s., 1H), 8.29 - 8.26 (m, 1H), 7.92 - 7.87 (m, 3H), 7.61 (d, J=7.9 Hz, 1H), 5.57 (br. s., 2H), 5.23 (quin, J=6.6 Hz, 1H), 5.08 - 5.01 (m, 1H), 4.70 (d, J=11.9 Hz, 1H), 4.54 - 4.48 (m, 1H), 3.92 - 3.88 (m, 1H), 3.69 (dd, J=10.5, 8.4 Hz, 1H), 2.92 (d, J=10.1 Hz, 1H), 2.70 (d, J=7.6 Hz, 1H), 2.64 (d, J=13.4 Hz, 1H), 2.38 - 2.25 (m, 2H), 1.92 (s, 1H), 1.87 - 1.79 (m, 1H), 1.67 (d, J=9.5 Hz, 1H), 1.63 (br. s., 1H), 1.53 (t, J=19.5 Hz, 4H), 1.45 (br. s., 1H), 1.42 - 1.39 (m, 1H), 1.35 (d, J=6.4 Hz, 6H), 1.23 (s, 3H), 1.16 (br. s., 3H), 1.02 (br. s., 2H), 0.94 (d, J=7.0 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H), 0.81 (s, 3H), 0.75 (t, J=13.1 Hz, 1H). MS: MS *m/z* 833.46 (M^++1).

Preparation of Compounds 1019 and 1020



Compound 1019



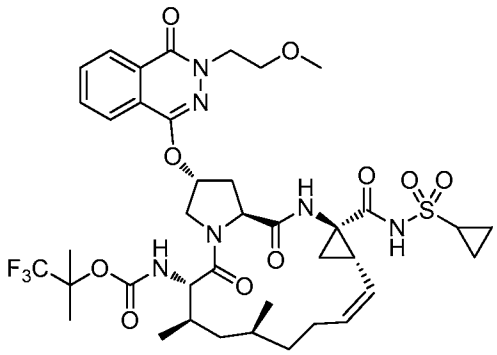
Compound 1020

Compounds 1019 and 1020 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

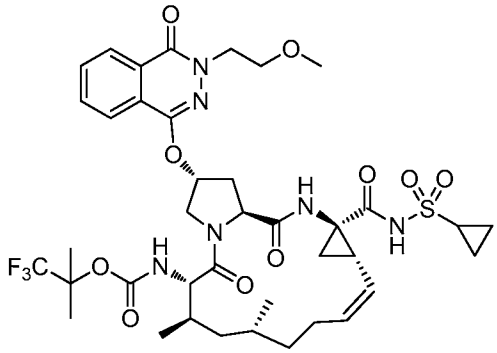
Compound 1019: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(2-methoxyethyl)-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 863.51 (M^++1).

Compound 1020: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(2-methoxyethyl)-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.05 (br. s., 1H), 9.16 (br. s., 1H), 8.29 - 8.25 (m, 1H), 7.94 - 7.89 (m, 4H), 7.62 (d, J=7.0 Hz, 1H), 5.54 (br. s., 2H), 4.98 (br. s., 1H), 4.66 (br. s., 1H), 4.50 (br. s., 1H), 4.24 (t, J=5.3 Hz, 2H), 3.89 (d, J=8.5 Hz, 1H), 3.78 - 3.68 (m, 4H), 3.28 (s, 3H), 2.65 (br. s., 2H), 2.37 - 2.27 (m, 2H), 1.89 (br. s., 1H), 1.82 (d, J=5.8 Hz, 1H), 1.69 (br. s., 1H), 1.57 (t, J=19.7 Hz, 5H), 1.41 (br. s., 3H), 1.25 (s, 3H), 1.16 (br. s., 2H), 0.91 (d, J=14.6 Hz, 7H), 0.95 - 0.89 (m, J=15.3 Hz, 5H), 0.76 (br. s., 1H). MS: MS *m/z* 863.51 (M^++1).

Preparation of Compounds 1021 and 1022



Compound 1021



Compound 1022

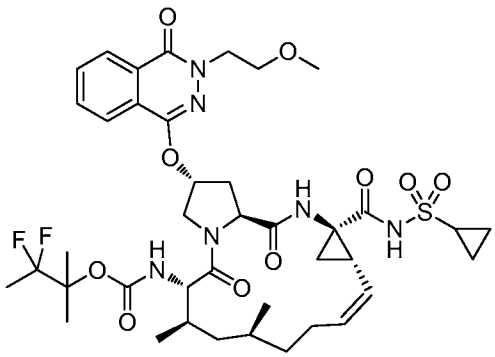
Compounds 1021 and 1022 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1021: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(2-methoxyethyl)-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-

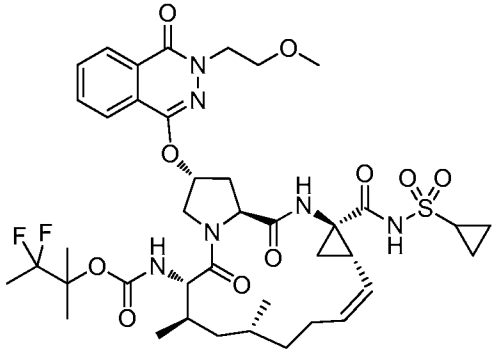
1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 853.5 (M^++1).

Compound 1022: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(2-methoxyethyl)-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.20 (br. s., 1H), 9.04 (br. s., 1H), 8.29 - 8.25 (m, 1H), 7.94 - 7.88 (m, 4H), 7.82 (br. s., 1H), 5.53 (br. s., 2H), 5.07 (br. s., 1H), 4.64 (br. s., 1H), 4.48 (br. s., 1H), 4.29 - 4.18 (m, 2H), 3.86 (d, J=8.5 Hz, 1H), 3.76 - 3.72 (m, 2H), 3.71 - 3.65 (m, 2H), 3.27 (s, 3H), 2.63 (d, J=16.8 Hz, 2H), 2.35 - 2.23 (m, 2H), 1.89 (br. s., 1H), 1.83 (br. s., 1H), 1.73 (br. s., 1H), 1.59 (br. s., 1H), 1.52 (br. s., 1H), 1.40 (br. s., 1H), 1.35 (br. s., 1H), 1.33 (s, 3H), 1.25 (s, 1H), 1.16 (br. s., 1H), 1.07 (br. s., 2H), 1.01 (s, 3H), 0.93 (d, J=6.7 Hz, 3H), 0.89 (d, J=6.1 Hz, 3H), 0.73 (br. s., 1H). MS: MS *m/z* 853.5 (M^++1).

Preparation of Compounds 1023 and 1024



Compound 1023



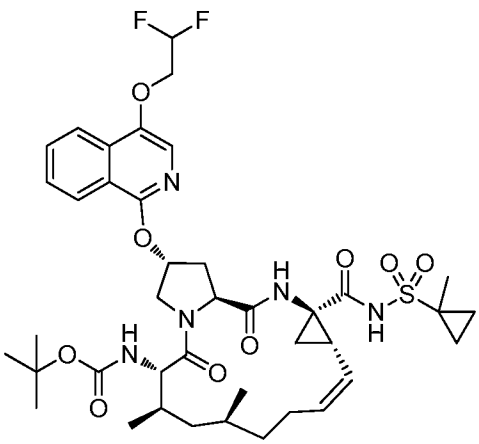
Compound 1024

Compounds 1023 and 1024 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

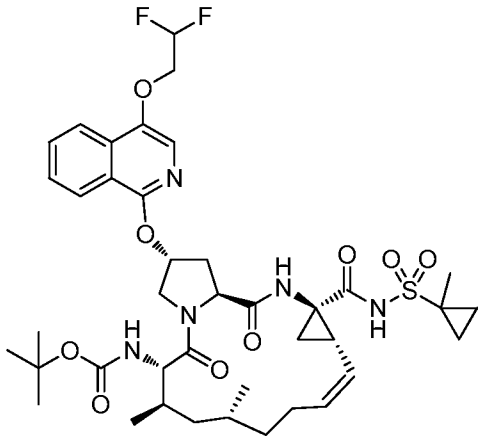
Compound 1023: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(2-methoxyethyl)-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 849.6 (M^++1).

Compound 1024: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(2-methoxyethyl)-4-oxo-3,4-dihydrophthalazin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.20 (br. s., 1H), 9.03 (br. s., 1H), 8.29 - 8.25 (m, 1H), 7.95 - 7.89 (m, 3H), 7.61 (d, J=7.9 Hz, 1H), 5.54 (br. s., 2H), 5.05 (br. s., 1H), 4.66 (d, J=10.4 Hz, 1H), 4.48 (br. s., 1H), 4.27 - 4.19 (m, 2H), 3.87 (dd, J=11.4, 3.2 Hz, 1H), 3.79 - 3.68 (m, 3H), 3.28 (s, 3H), 2.91 (br. s., 1H), 2.65 (br. s., 2H), 2.36 - 2.25 (m, 2H), 1.95 - 1.86 (m, 1H), 1.82 (d, J=6.1 Hz, 1H), 1.70 (br. s., 1H), 1.57 (t, J=19.7 Hz, 5H), 1.44 (br. s., 1H), 1.37 (br. s., 1H), 1.28 - 1.22 (m, 4H), 1.14 (br. s., 3H), 0.96 - 0.89 (m, 10H), 0.76 (d, J=10.1 Hz, 1H). MS: MS *m/z* 849.6 (M^++1).

Preparation of Compounds 1025 and 1026



Compound 1025



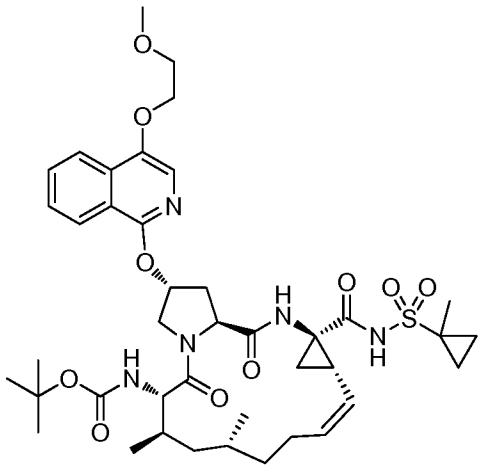
Compound 1026

Compounds 1025 and 1026 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1025: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 818.8 (M^++1).

Compound 1026: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.06 (br. s., 1H), 9.11 (br. s., 1H), 8.16 - 8.04 (m, 2H), 7.88 - 7.81 (m, 1H), 7.79 - 7.72 (m, 1H), 7.62 (t, J=7.6 Hz, 1H), 7.17 (d, J=7.3 Hz, 1H), 6.67 - 6.39 (m, 1H), 5.78 (br. s., 1H), 5.52 (br. s., 1H), 4.97 (br. s., 1H), 4.62 (d, J=11.0 Hz, 1H), 4.50 (tdd, J=14.5, 6.2, 3.4 Hz, 3H), 3.94 - 3.89 (m, 1H), 3.78 - 3.68 (m, 1H), 2.91 (s, 1H), 2.75 (s, 1H), 2.71 (br. s., 1H), 2.61 (br. s., 1H), 2.35 - 2.26 (m, 2H), 1.94 - 1.86 (m, 1H), 1.82 (d, J=5.8 Hz, 1H), 1.70 (br. s., 1H), 1.61 (br. s., 1H), 1.50 (br. s., 1H), 1.44 - 1.36 (m, 4H), 1.27 - 1.22 (m, 1H), 1.14 - 1.06 (m, 9H), 1.04 (br. s., 1H), 0.93 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.4 Hz, 3H), 0.73 (t, J=12.2 Hz, 1H). MS: MS *m/z* 818.8 (M^++1).

Preparation of Compound 1027

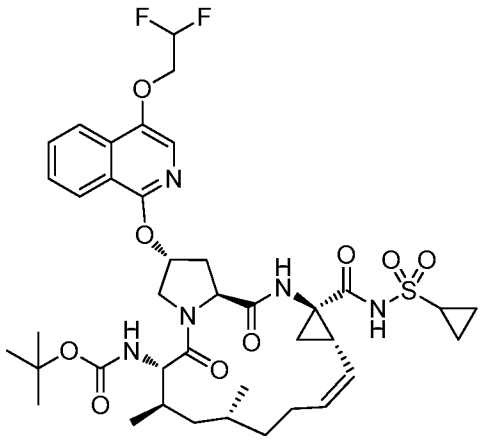


Compound 1027

Compound 1027 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1027: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.05 (br. s., 1H), 9.10 (br. s., 1H), 8.13 - 8.05 (m, 2H), 7.80 (t, J=7.6 Hz, 1H), 7.68 (s, 1H), 7.60 (t, J=7.6 Hz, 1H), 7.17 (d, J=7.9 Hz, 1H), 5.77 (br. s., 1H), 5.52 (br. s., 1H), 4.97 (br. s., 1H), 4.60 (d, J=11.0 Hz, 1H), 4.51 - 4.45 (m, 1H), 4.28 (dd, J=5.3, 3.2 Hz, 2H), 3.94 - 3.89 (m, 1H), 3.81 - 3.76 (m, 2H), 3.72 (dd, J=10.7, 8.5 Hz, 1H), 3.18 (d, J=5.2 Hz, 1H), 2.91 (s, 1H), 2.75 (s, 1H), 2.74 - 2.66 (m, J=6.7 Hz, 1H), 2.66 - 2.56 (m, 1H), 2.39 - 2.23 (m, 2H), 1.95 - 1.86 (m, 1H), 1.86 - 1.76 (m, J=6.1 Hz, 1H), 1.70 (dd, J=12.4, 6.3 Hz, 1H), 1.61 (br. s., 1H), 1.51 (br. s., 1H), 1.48 - 1.43 (m, 2H), 1.41 (s, 3H), 1.39 - 1.32 (m, 1H), 1.32 - 1.14 (m, 3H), 1.12 (s, 9H), 1.09 - 0.96 (m, 1H), 0.93 (d, J=6.7 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H), 0.74 (t, J=12.2 Hz, 1H). MS: MS *m/z* 812.8 (M^++1).

Preparation of Compound 1028

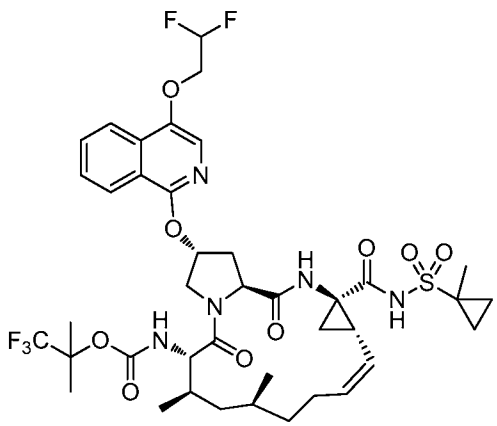


Compound 1028

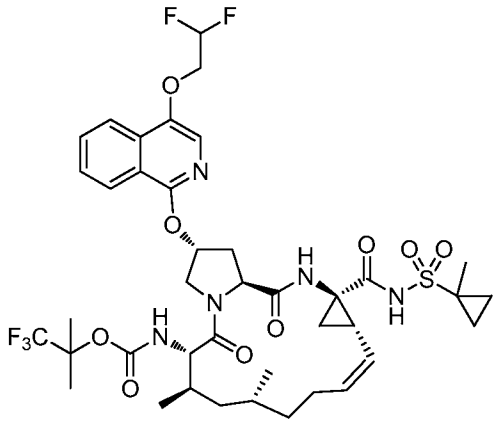
Compound 1028 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1028: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.20 (br. s., 1H), 8.97 (br. s., 1H), 8.16 - 8.04 (m, 2H), 7.88 - 7.81 (m, 1H), 7.77 (s, 1H), 7.62 (t, J=7.6 Hz, 1H), 7.16 (d, J=7.9 Hz, 1H), 6.67 - 6.38 (m, 1H), 5.77 (br. s., 1H), 5.51 (br. s., 1H), 5.05 (br. s., 1H), 4.61 (d, J=10.1 Hz, 1H), 4.56 - 4.41 (m, 3H), 3.94 - 3.87 (m, 1H), 3.79 - 3.68 (m, 1H), 2.91 (s, 2H), 2.75 (s, 1H), 2.61 (br. s., 2H), 2.35 - 2.25 (m, 2H), 1.95 - 1.86 (m, 1H), 1.81 (d, J=5.5 Hz, 1H), 1.72 (br. s., 1H), 1.59 (br. s., 1H), 1.53 (br. s., 1H), 1.42 (br. s., 1H), 1.40 - 1.31 (m, 1H), 1.25 (br. s., 1H), 1.14 - 1.09 (m, 9H), 1.05 (br. s., 1H), 0.99 (br. s., 1H), 0.94 (d, J=7.0 Hz, 3H), 0.88 (d, J=6.1 Hz, 3H), 0.72 (t, J=12.8 Hz, 1H). MS: MS *m/z* 804.8 (M^++1).

Preparation of Compounds 1029 and 1030



Compound 1029



Compound 1030

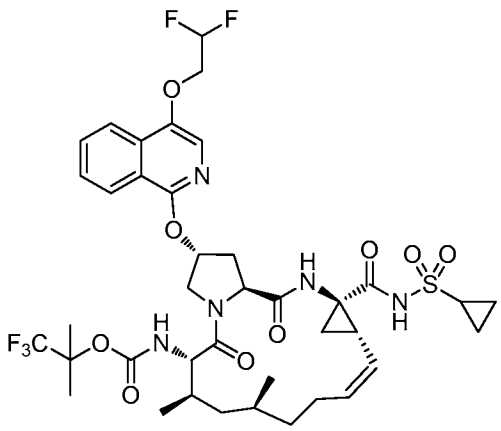
Compounds 1029 and 1030 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1029: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 872.7 (M^++1).

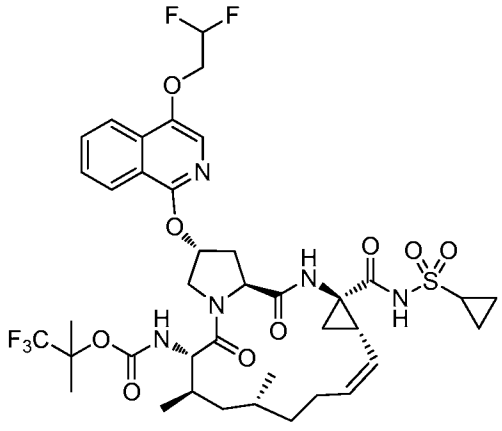
Compound 1030: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.06 (br. s., 1H), 9.14 (br. s., 1H), 8.13 - 8.05 (m, 2H), 7.86 - 7.79 (m, 2H), 7.79 - 7.75 (m, 1H), 7.66 (t, J=7.5 Hz, 1H), 6.69 - 6.38 (m, 1H), 5.79 (br. s., 1H), 5.52 (br. s., 1H), 4.99 (br. s., 1H), 4.60 - 4.43 (m, 4H), 3.95 - 3.88 (m, 1H), 3.69 (dd, J=10.7, 8.2 Hz, 1H), 2.91 (s, 2H), 2.75 (s, 2H), 2.65 (br. s., 1H), 2.61 (br. s., 1H), 2.39 - 2.28 (m, 2H), 1.94 - 1.87 (m, 1H), 1.84 (d, J=6.7 Hz, 1H), 1.71 (br. s., 1H), 1.64 - 1.57 (m, 1H), 1.50 (br. s., 1H), 1.41 (br. s., 4H), 1.32 (s, 3H), 1.26 (d, J=13.7 Hz, 1H), 1.18 (d,

J=11.6 Hz, 1H), 1.01 (s, 3H), 0.93 (d, J=6.7 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H), 0.79 - 0.70 (m, 1H). MS: MS *m/z* 872.7 (M^++1).

Preparation of Compounds 1031 and 1032



Compound 1031



Compound 1032

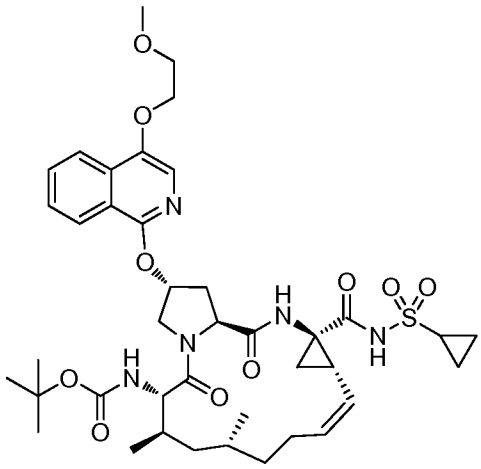
Compounds 1031 and 1032 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1031: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 858.7 (M^++1).

Compound 1032: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.20 (br. s., 1H), 9.02 (br. s., 1H), 8.13 - 8.05 (m, 2H), 7.87 - 7.79 (m, 2H), 7.78 (s, 1H), 7.65 (t, J=7.6 Hz, 1H), 6.70 - 6.37 (m, 1H), 5.77 (br. s., 1H), 5.52 (br. s., 1H), 5.06 (br. s., 1H), 4.60 - 4.42 (m, 4H), 3.92 - 3.87 (m, 1H), 3.69 (dd, J=10.7, 7.9 Hz,

1H), 2.95 - 2.91 (m, 1H), 2.65 (d, J=1.8 Hz, 1H), 2.61 (br. s., 1H), 2.36 - 2.27 (m, 2H), 1.94 - 1.80 (m, 2H), 1.72 (br. s., 1H), 1.60 (br. s., 1H), 1.51 (br. s., 1H), 1.42 (br. s., 2H), 1.33 (s, 3H), 1.26 - 1.18 (m, 1H), 1.12 (br. s., 2H), 1.04 (s, 3H), 1.00 (br. s., 2H), 0.94 (d, J=6.7 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H), 0.73 (br. s., 1H). MS: MS *m/z* 858.7 (M^++1).

Preparation of Compound 1033



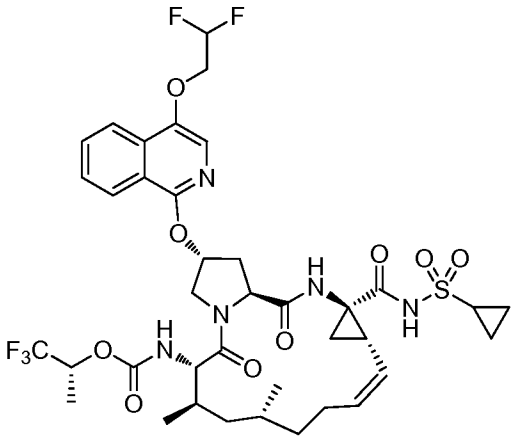
Compound 1033

Compound 1033 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1033: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.19 (br. s., 1H), 8.97 (br. s., 1H), 8.14 - 8.05 (m, 2H), 7.80 (t, J=7.6 Hz, 1H), 7.68 (s, 1H), 7.60 (t, J=7.6 Hz, 1H), 7.17 (br. s., 1H), 5.75 (br. s., 1H), 5.52 (br. s., 1H), 5.05 (br. s., 1H), 4.59 (br. s., 1H), 4.43 (br. s., 1H), 4.28 (dd, J=5.5, 3.1 Hz, 2H), 3.92 - 3.87 (m, 1H), 3.82 - 3.77 (m, 2H), 3.73 (t, J=9.6 Hz, 1H), 3.38 (s, 3H), 2.72 - 2.59 (m, 2H), 2.34 - 2.25 (m, 2H), 1.95 - 1.85 (m, 1H), 1.81 (br. s., 1H), 1.71 (br. s., 1H), 1.59 (br. s., 1H), 1.54 (br. s., 2H), 1.42 (br. s., 1H), 1.36 (br. s., 1H), 1.25 (d, J=6.1 Hz, 2H), 1.14 (s, 9H), 1.05 (br. s., 1H), 1.01 (br. s.,

1H), 0.93 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.1 Hz, 3H), 0.72 (br. s., 1H). MS: MS *m/z* 798.65 (M^++1).

Preparation of Compound 1034

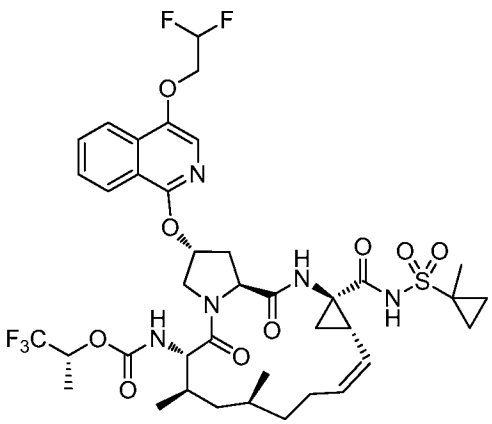


Compound 1034

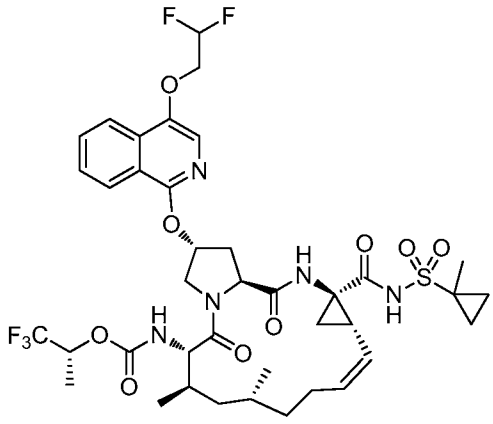
Compound 1034 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1034: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.18 (s, 1H), 8.98 (br. s., 1H), 8.07 (dd, J=8.2, 4.3 Hz, 2H), 7.87 - 7.81 (m, 1H), 7.77 (s, 1H), 7.60 (t, J=7.5 Hz, 1H), 6.68 - 6.37 (m, 1H), 5.79 (br. s., 1H), 5.53 (d, J=5.5 Hz, 1H), 5.06 (t, J=9.5 Hz, 1H), 4.71 - 4.65 (m, 1H), 4.56 - 4.43 (m, 4H), 3.95 - 3.90 (m, 1H), 3.77 (dd, J=10.7, 8.2 Hz, 1H), 2.95 - 2.88 (m, 1H), 2.70 - 2.59 (m, 2H), 2.39 - 2.27 (m, 2H), 1.96 - 1.82 (m, 2H), 1.71 (br. s., 1H), 1.63 - 1.52 (m, 2H), 1.44 (br. s., 1H), 1.41 - 1.31 (m, 1H), 1.19 (d, J=6.7 Hz, 3H), 1.12 (d, J=6.7 Hz, 3H), 0.99 (br. s., 3H), 0.94 (d, J=6.7 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.76 (t, J=12.4 Hz, 1H). MS: MS *m/z* 798.65 (M^++1).

Preparation of Compounds 1035 and 1036



Compound 1035



Compound 1036

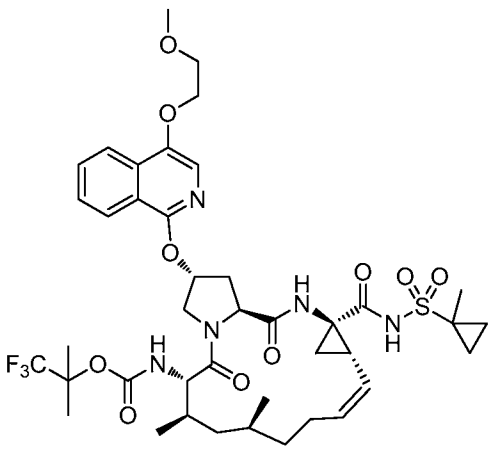
Compounds 1035 and 1036 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1035: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 798.65 (M^++1).

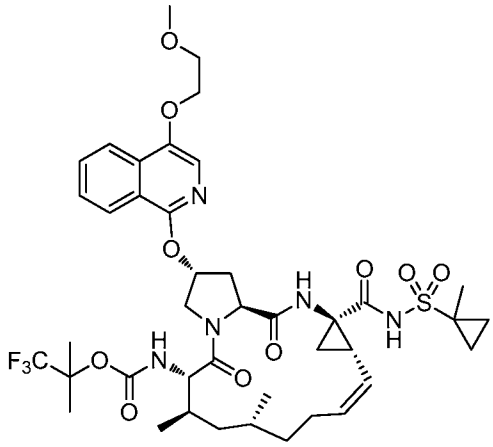
Compound 1036: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.04 (br. s., 1H), 9.11 (br. s., 1H), 8.11 - 8.04 (m, 3H), 7.83 (t, J=8.2 Hz, 1H), 7.77 (s, 1H), 7.60 (t, J=7.6 Hz, 1H), 6.69 - 6.39 (m, 1H), 5.80 (br. s., 1H), 5.52 (br. s., 1H), 4.99 (br. s., 1H), 4.65 (br. s., 1H), 4.51 (td, J=14.5, 3.4 Hz, 4H), 3.95 (dd, J=11.3, 3.4 Hz, 1H), 3.77 (dd, J=10.5, 8.1 Hz, 1H), 2.63 (d, J=19.8 Hz, 2H), 2.31 (t, J=9.8 Hz, 2H), 1.95 - 1.90 (m, 1H), 1.90 - 1.79 (m, 1H), 1.70 (br. s., 1H), 1.60 (br. s., 1H), 1.51 (br. s., 1H), 1.48 - 1.31 (m, 6H), 1.28 (br. s., 1H), 1.19 (s, 3H), 1.14 - 1.09 (m, 1H),

0.93 (d, J=6.7 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.88 - 0.82 (m, 2H), 0.76 (br. s., 1H). MS: MS *m/z* 798.65 (M^++1).

Preparation of Compounds 1037 and 1038



Compound 1037



Compound 1038

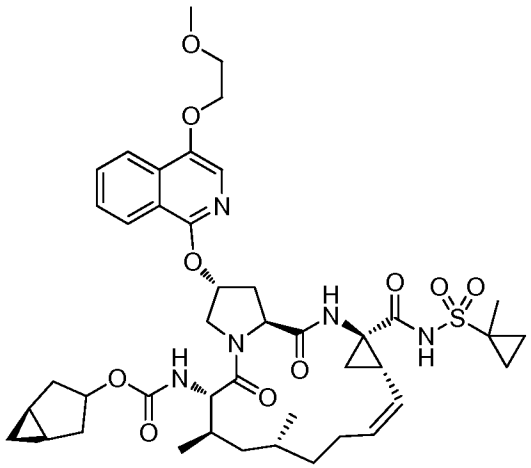
Compounds 1037 and 1038 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1037: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 866.66 (M^++1).

Compound 1038: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.06 (br. s., 1H), 9.14 (s, 1H), 8.09 (t, J=9.0 Hz, 2H), 7.83 - 7.77 (m, 2H), 7.69 (s, 1H), 7.63 (t, J=7.6 Hz, 1H), 5.76 (br. s., 1H), 5.47 (br. s., 1H), 4.99 (s, 1H), 4.50 (br. s., 2H), 4.28 (d, J=3.1 Hz, 2H), 3.93 - 3.89 (m, 1H), 3.81 - 3.78 (m, 2H), 3.73 - 3.68

(m, 1H), 2.31 (t, J=9.9 Hz, 2H), 1.84 (br. s., 2H), 1.75 (br. s., 1H), 1.50 (br. s., 1H), 1.44 - 1.30 (m, 12H), 1.25 (br. s., 2H), 1.20 (br. s., 3H), 1.05 (s, 3H), 0.93 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.1 Hz, 3H), 0.72 (br. s., 1H). MS: MS *m/z* 866.66 (M^++1).

Preparation of Compound 1039

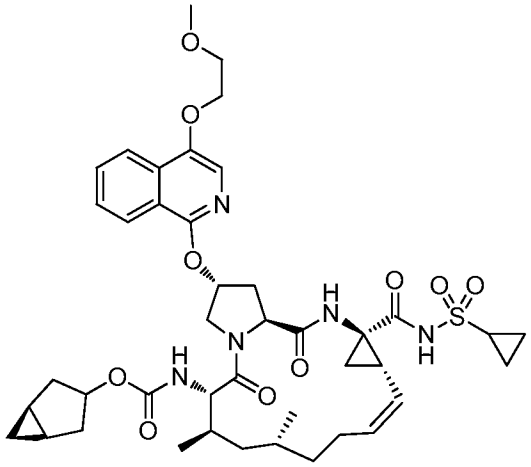


Compound 1039

Compound 1039 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1039: (1S,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 8.09 (t, J=9.2 Hz, 2H), 7.82 (t, J=7.6 Hz, 1H), 7.70 - 7.63 (m, 2H), 7.35 (d, J=8.2 Hz, 1H), 5.76 (br. s., 1H), 5.40 (br. s., 1H), 4.61 (t, J=6.6 Hz, 1H), 4.42 (br. s., 2H), 4.31 - 4.26 (m, 2H), 3.96 - 3.91 (m, 1H), 3.82 - 3.73 (m, 3H), 2.35 - 2.20 (m, 2H), 1.97 - 1.86 (m, 3H), 1.86 - 1.69 (m, 3H), 1.56 (d, J=14.3 Hz, 1H), 1.47 (br. s., 1H), 1.41 - 1.22 (m, 8H), 1.22 - 1.14 (m, 2H), 1.14 - 1.06 (m, 2H), 1.05 - 0.95 (m, 1H), 0.92 (d, J=6.7 Hz, 3H), 0.86 (d, J=6.4 Hz, 3H), 0.67 (br. s., 1H), 0.60 - 0.41 (m, 1H), 0.37 - 0.28 (m, 2H). MS: MS *m/z* 836.71 (M^++1).

Preparation of Compound 1040

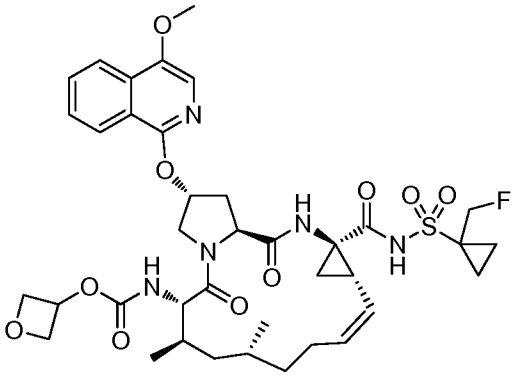


Compound 1040

Compound 1040 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1040: (1S,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.21 (br. s., 1H), 8.09 (t, J=8.5 Hz, 2H), 7.82 (t, J=7.6 Hz, 1H), 7.71 - 7.62 (m, 2H), 7.36 (br. s., 1H), 5.76 (br. s., 1H), 5.45 (br. s., 1H), 4.62 (t, J=6.7 Hz, 1H), 4.42 (br. s., 2H), 4.31 - 4.26 (m, 2H), 3.94 - 3.90 (m, 1H), 3.81 - 3.73 (m, 3H), 2.35 - 2.18 (m, 3H), 1.99 - 1.87 (m, 3H), 1.87 - 1.66 (m, 4H), 1.66 - 1.46 (m, 3H), 1.41 (br. s., 2H), 1.32 (d, J=14.3 Hz, 3H), 1.28 - 1.15 (m, 3H), 1.11 (t, J=11.6 Hz, 2H), 0.93 (d, J=6.4 Hz, 3H), 0.86 (d, J=6.4 Hz, 3H), 0.69 (br. s., 3H), 0.38 - 0.29 (m, 2H). MS: MS *m/z* 822.74 (M^++1).

Preparation of Compound 1041

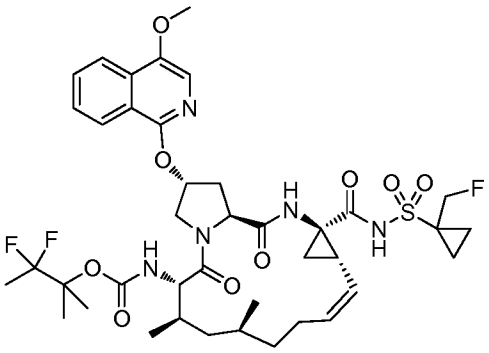


Compound 1041

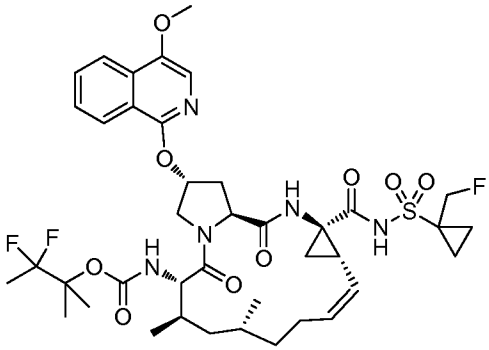
Compound 1041 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1041: oxetan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.27 (s, 1H), 9.02 (s, 1H), 8.08 (t, J=7.8 Hz, 2H), 7.87 - 7.79 (m, 2H), 7.72 - 7.64 (m, 2H), 5.78 (br. s., 1H), 5.55 - 5.48 (m, 1H), 5.01 (t, J=9.9 Hz, 1H), 4.86 (d, J=11.6 Hz, 2H), 4.59 (d, J=11.6 Hz, 1H), 4.55 - 4.43 (m, 3H), 4.38 (t, J=6.9 Hz, 1H), 4.32 - 4.26 (m, 1H), 4.13 - 4.06 (m, 1H), 3.99 (s, 3H), 3.96 - 3.87 (m, 2H), 3.76 - 3.70 (m, 1H), 2.71 - 2.58 (m, 2H), 2.39 - 2.23 (m, 2H), 1.96 - 1.80 (m, 2H), 1.68 (dd, J=12.5, 7.0 Hz, 1H), 1.53 (br. s., 4H), 1.44 (br. s., 1H), 1.42 - 1.32 (m, 1H), 1.32 - 1.18 (m, 1H), 1.14 (d, J=12.5 Hz, 1H), 0.94 (d, J=6.7 Hz, 3H), 0.90 (d, J=6.1 Hz, 3H), 0.75 (t, J=12.4 Hz, 1H). MS: MS *m/z* 786.5 (M^++1).

Preparation of Compounds 1042 1nd 1043



Compound 1042



Compound 1043

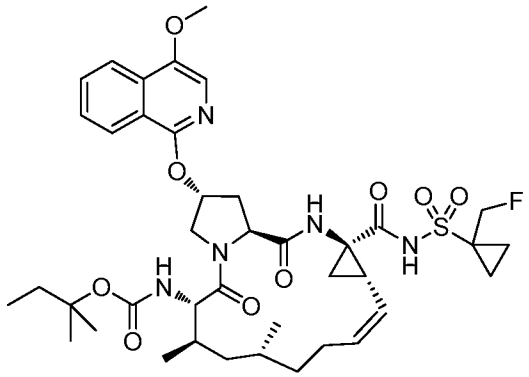
Compounds 1042 and 1043 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1042: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 786.5 (M^++1).

Compound 1043: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.29 (s, 1H), 9.04 (s, 1H), 8.07 (d, J=8.2 Hz, 1H), 8.10 (d, J=8.5 Hz, 1H), 7.80 (t, J=7.6 Hz, 1H), 7.66 (s, 1H), 7.65 - 7.59 (m, 2H), 5.77 (br. s., 1H), 5.55 - 5.49 (m, 1H), 5.00 (t, J=10.1 Hz, 1H), 4.91 - 4.66 (m, J=11.6 Hz, 1H), 4.57 (dd, J=16.6, 11.7 Hz, 1H), 4.53 - 4.45 (m, 2H), 3.98 (s, 3H), 3.96 - 3.89 (m, 1H), 3.75 - 3.70 (m, 1H), 2.72 - 2.59 (m, 2H), 2.39 - 2.27 (m, 2H), 1.94 - 1.78 (m, 2H), 1.70 (dd, J=12.1, 6.9 Hz, 1H), 1.64 - 1.49 (m, 7H), 1.43 (br. s., 1H), 1.41 - 1.29 (m, 1H), 1.27 (s, 3H), 1.24 - 1.19 (m, 1H), 1.15 (d, J=12.2 Hz, 1H), 1.01 (s, 3H), 0.94

(d, J=6.7 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.76 (t, J=12.7 Hz, 1H). MS: MS *m/z* 786.5 (M^++1).

Preparation of Compound 1044

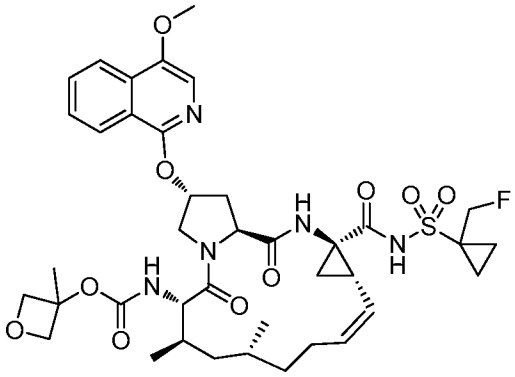


Compound 1044

Compound 1044 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1044: tert-pentyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.29 (s, 1H), 9.03 (br. s., 1H), 8.12 - 8.05 (m, 2H), 7.79 (t, J=7.5 Hz, 1H), 7.66 (s, 1H), 7.60 (t, J=7.6 Hz, 1H), 7.19 (d, J=7.9 Hz, 1H), 5.76 (br. s., 1H), 5.51 (br. s., 1H), 4.98 (t, J=9.3 Hz, 1H), 4.90 - 4.69 (m, 1H), 4.59 (d, J=11.0 Hz, 1H), 4.52 - 4.42 (m, 1H), 3.98 (s, 3H), 3.95 - 3.88 (m, 1H), 3.76 - 3.71 (m, 1H), 2.71 - 2.63 (m, 1H), 2.60 (br. s., 1H), 2.35 - 2.24 (m, 2H), 1.93 - 1.87 (m, 1H), 1.83 (d, J=6.4 Hz, 1H), 1.69 (br. s., 1H), 1.58 - 1.36 (m, 6H), 1.34 (br. s., 1H), 1.24 (d, J=13.1 Hz, 3H), 1.14 (d, J=11.0 Hz, 1H), 1.07 (s, 3H), 1.10 (s, 3H), 0.94 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.4 Hz, 3H), 0.81 - 0.70 (m, 2H), 0.68 (t, J=7.5 Hz, 3H). MS: MS *m/z* 800.5 (M^++1).

Preparation of Compound 1045

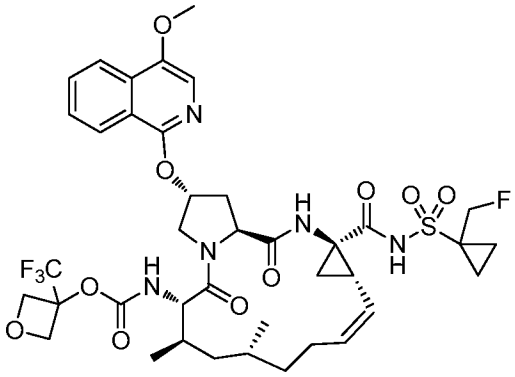


Compound 1045

Compound 1045 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1045: 3-methyloxetan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, METHANOL-d4) Shift 8.17 - 8.10 (m, 2H), 7.78 - 7.71 (m, 1H), 7.64 - 7.53 (m, 2H), 5.79 (br. s., 1H), 5.53 (td, J=10.2, 5.8 Hz, 1H), 5.16 (br. s., 1H), 4.87 - 4.74 (m, 1H), 4.72 - 4.52 (m, 3H), 4.49 (d, J=7.0 Hz, 1H), 4.28 (d, J=7.0 Hz, 1H), 4.11 (d, J=7.0 Hz, 1H), 4.02 (s, 3H), 4.01 - 3.95 (m, 2H), 3.84 (d, J=10.7 Hz, 1H), 2.72 (dd, J=13.7, 7.0 Hz, 1H), 2.62 (q, J=9.0 Hz, 1H), 2.49 - 2.35 (m, 2H), 1.95 - 1.77 (m, 3H), 1.69 (dd, J=8.4, 5.3 Hz, 1H), 1.62 (td, J=10.2, 4.6 Hz, 2H), 1.54 (dd, J=9.5, 5.2 Hz, 1H), 1.50 - 1.38 (m, 2H), 1.32 - 1.23 (m, 1H), 1.22 (s, 3H), 1.21 - 1.08 (m, 2H), 1.01 (d, J=7.0 Hz, 3H), 0.99 (d, J=6.4 Hz, 3H), 0.89 - 0.78 (m, 1H). MS: MS *m/z* 800.4 (M^++1).

Preparation of Compound 1046

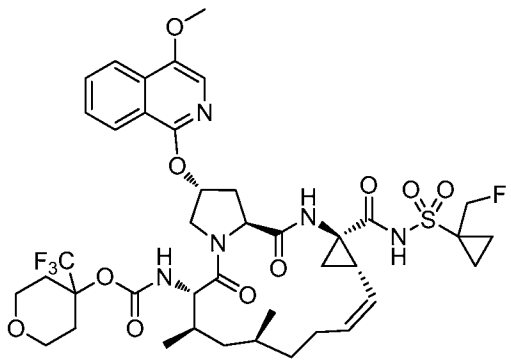


Compound 1046

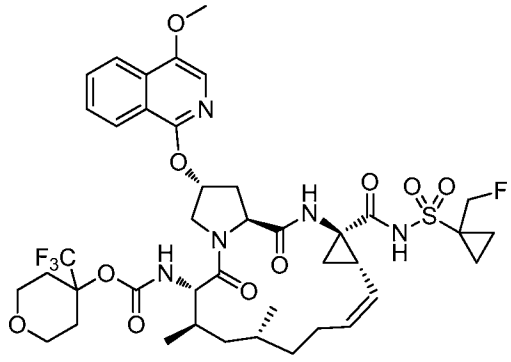
Compound 1046 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1046: 3-(trifluoromethyl)oxetan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.28 (s, 1H), 9.05 (s, 1H), 8.09 - 8.01 (m, 3H), 7.81 (t, J=7.5 Hz, 1H), 7.65 (s, 1H), 7.64 - 7.59 (m, 1H), 5.74 (br. s., 1H), 5.56 - 5.49 (m, 1H), 5.00 (t, J=9.9 Hz, 1H), 4.89 - 4.74 (m, J=11.6 Hz, 1H), 4.59 (d, J=11.3 Hz, 1H), 4.48 (ddd, J=17.2, 10.8, 6.7 Hz, 2H), 3.97 (s, 3H), 3.96 - 3.91 (m, 1H), 3.82 - 3.76 (m, 1H), 3.72 (d, J=7.9 Hz, 1H), 3.41 (t, J=10.4 Hz, 2H), 3.24 - 3.17 (m, 1H), 2.71 - 2.60 (m, 2H), 2.39 - 2.26 (m, 2H), 2.05 (d, J=12.2 Hz, 1H), 1.96 - 1.81 (m, 3H), 1.75 - 1.62 (m, 2H), 1.58 - 1.48 (m, 5H), 1.44 (br. s., 1H), 1.42 - 1.32 (m, 1H), 1.32 - 1.19 (m, 2H), 1.15 (d, J=11.9 Hz, 1H), 0.95 (d, J=7.0 Hz, 3H), 0.92 (d, J=6.4 Hz, 3H), 0.77 (t, J=12.4 Hz, 1H). MS: MS *m/z* 854.3 (M^++1).

Preparation of Compounds 1047 and 1048



Compound 1047



Compound 1048

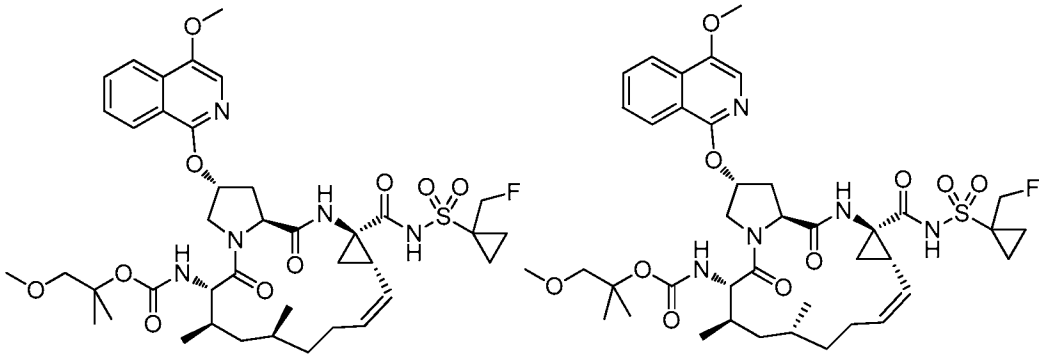
Compounds 1047 and 1048 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1047: 4-(trifluoromethyl)tetrahydro-2H-pyran-4-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 882.4 (M^++1).

Compound 1048: 4-(trifluoromethyl)tetrahydro-2H-pyran-4-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.28 (s, 1H), 9.05 (s, 1H), 8.09 - 8.01 (m, 3H), 7.81 (t, J=7.5 Hz, 1H), 7.65 (s, 1H), 7.64 - 7.59 (m, 1H), 5.74 (br. s., 1H), 5.56 - 5.49 (m, 1H), 5.00 (t, J=9.9 Hz, 1H), 4.89 - 4.74 (m, J=11.6 Hz, 1H), 4.59 (d, J=11.3 Hz, 1H), 4.48 (ddd, J=17.2, 10.8, 6.7 Hz, 2H), 3.97 (s, 3H), 3.96 - 3.91 (m, 1H), 3.82 - 3.76 (m, 1H), 3.72 (d, J=7.9 Hz, 1H), 3.41 (t, J=10.4 Hz, 2H), 3.24 - 3.17 (m, 1H), 2.71 - 2.60 (m, 2H), 2.39 - 2.26 (m, 2H), 2.05 (d, J=12.2 Hz, 1H), 1.96 - 1.81 (m,

3H), 1.75 - 1.62 (m, 2H), 1.58 - 1.48 (m, 5H), 1.44 (br. s., 1H), 1.42 - 1.32 (m, 1H), 1.32 - 1.19 (m, 2H), 1.15 (d, J=11.9 Hz, 1H), 0.95 (d, J=7.0 Hz, 3H), 0.92 (d, J=6.4 Hz, 3H), 0.77 (t, J=12.4 Hz, 1H). MS: MS *m/z* 882.4 (M^++1).

Preparation of Compounds 1049 and 1050



Compound 1049 Compound 1050

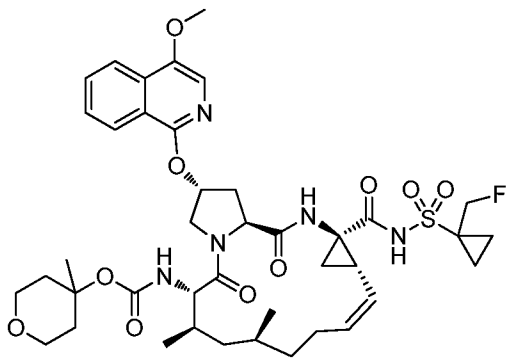
Compounds 1049 and 1050 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1049: 1-methoxy-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 816.7 (M^++1).

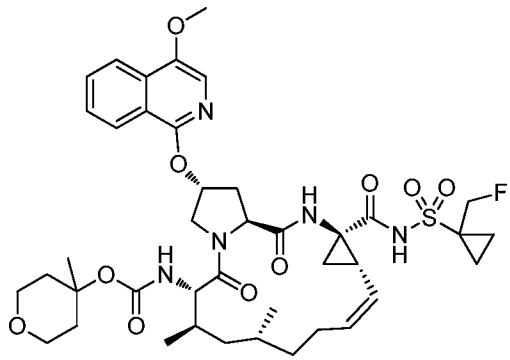
Compound 1050: 1-methoxy-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.29 (s, 1H), 9.04 (br. s., 1H), 8.12 (d, J=8.2 Hz, 1H), 8.06 (d, J=8.2 Hz, 1H), 7.79 (t, J=7.5 Hz, 1H), 7.66 (s, 1H), 7.61 (t, J=7.6 Hz, 1H), 7.28 (d, J=7.9 Hz, 1H), 5.76 (br. s., 1H), 5.52 (d, J=6.4 Hz, 1H), 4.98 (t,

J=9.5 Hz, 1H), 4.91 - 4.68 (m, 1H), 4.59 (d, J=11.0 Hz, 1H), 4.52 - 4.43 (m, 1H), 3.98 (s, 3H), 3.96 - 3.89 (m, 1H), 3.71 (dd, J=10.5, 8.4 Hz, 1H), 3.26 - 3.21 (m, 1H), 3.19 - 3.10 (m, 4H), 2.71 - 2.57 (m, 2H), 2.36 - 2.26 (m, 2H), 1.93 - 1.77 (m, 2H), 1.74 - 1.66 (m, 1H), 1.53 (br. s., 4H), 1.45 - 1.32 (m, 2H), 1.25 (d, J=12.8 Hz, 2H), 1.14 (d, J=13.1 Hz, 1H), 1.10 - 1.00 (m, 6H), 0.94 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.1 Hz, 3H), 0.73 (t, J=12.7 Hz, 1H). MS: MS *m/z* 816.7 (M^++1).

Preparation of Compounds 1051 and 1052



Compound 1051



Compound 1052

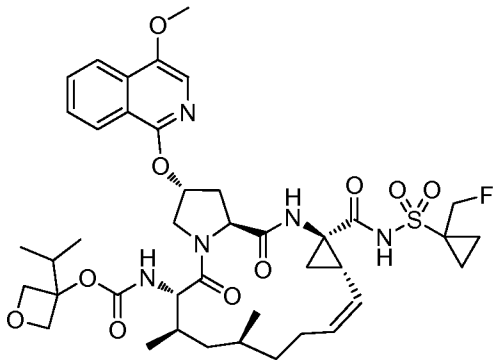
Compounds 1051 and 1052 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1051: 4-methyltetrahydro-2H-pyran-4-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 828.7 (M^++1).

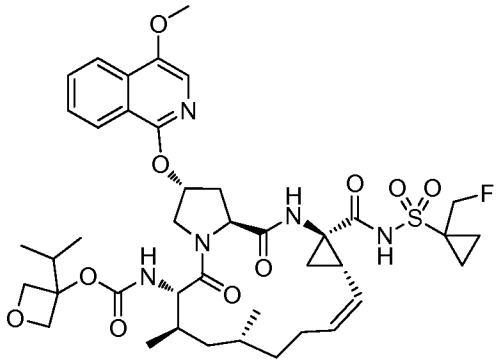
Compound 1052: 4-methyltetrahydro-2H-pyran-4-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 8.10 - 8.05 (m, 2H), 7.80 (t, J=7.6 Hz, 1H), 7.66 (s, 1H), 7.62 (t, J=7.8 Hz, 1H), 5.73 (br. s., 1H), 4.59 (br. s., 1H), 4.46 (br. s., 1H), 3.97 (s, 3H), 3.93 - 3.88 (m, 1H), 3.75 - 3.70 (m, 1H), 3.47 (d, J=3.7 Hz, 2H), 3.33 - 3.27 (m, 2H), 3.27 - 3.21 (m, 1H), 2.34 - 2.24 (m, 2H), 1.82 (br. s., 2H), 1.77 (d, J=14.0 Hz, 1H), 1.51 (d, J=15.3 Hz, 3H), 1.47 - 1.37 (m, 3H), 1.31 - 1.21 (m, 3H), 1.13 (s, 3H), 0.93 (d, J=6.7 Hz, 3H), 0.88 (d, J=5.8 Hz, 3H), 0.85 (br. s., 1H), 0.74 (br. s., 1H). MS: MS *m/z* 828.7 (M^++1).

Preparation of Compounds 1053 and 1054



Compound 1053



Compound 1054

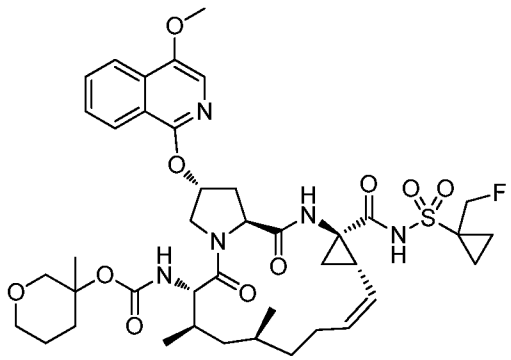
Compounds 1053 and 1054 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1053: 3-isopropyloxetan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 828.8 (M^++1).

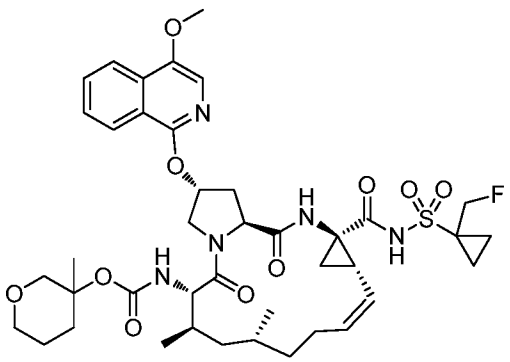
Compound 1054: 3-isopropyloxetan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.28 (s, 1H), 9.05 (br. s., 1H), 8.05 (d, J=8.5 Hz, 1H), 8.09 (d, J=8.2 Hz, 1H), 7.82 (t, J=7.6 Hz, 1H), 7.73 - 7.62 (m, 3H), 5.74 (br. s., 1H), 5.52 (d, J=6.1 Hz, 1H), 4.99 (t, J=9.8 Hz, 1H), 4.89 - 4.66 (m, 1H), 4.60 (d, J=11.0 Hz, 1H), 4.50 (d, J=11.3 Hz, 2H), 4.36 (d, J=7.3 Hz, 1H), 4.28 (d, J=7.3 Hz, 1H), 4.19 - 4.10 (m, 2H), 3.98 (s, 3H), 3.97 - 3.89 (m, 1H), 3.75 (dd, J=10.5, 8.7 Hz, 1H), 2.61 (d, J=6.1 Hz, 1H), 2.31 (ddd, J=13.7, 10.2, 4.1 Hz, 2H), 1.97 - 1.78 (m, 3H), 1.68 (d, J=5.8 Hz, 1H), 1.54 (br. s., 4H), 1.43 (br. s., 1H), 1.38 (br. s., 1H), 1.25 (d, J=12.5 Hz, 2H), 1.15 (br. s., 1H), 0.94 (d, J=6.7 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H), 0.82 (d, J=16.8 Hz, 1H), 0.77 (d, J=7.0 Hz, 3H), 0.75 - 0.66 (m, 2H), 0.67 - 0.58 (m, 3H). MS: MS *m/z* 828.8 (M^++1).

Preparation of Compounds 1055 and 1056



Compound 1055



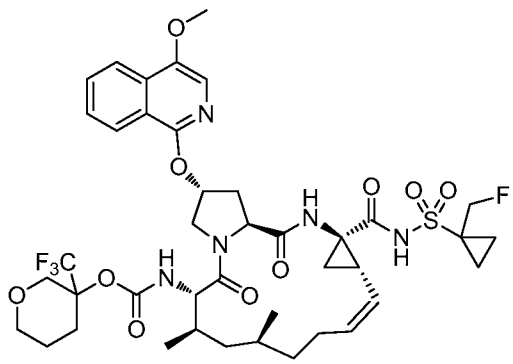
Compound 1056

Compounds 1055 and 1056 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

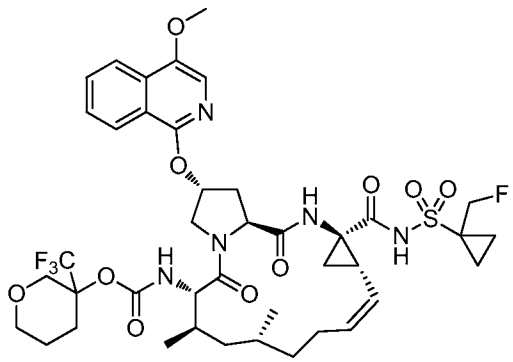
Compound 1055: 3-methyltetrahydro-2H-pyran-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 828.4 (M^++1).

Compound 1056: 3-methyltetrahydro-2H-pyran-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.28 (s, 1H), 9.01 (br. s., 1H), 8.12 (d, J=8.2 Hz, 1H), 8.10 - 8.04 (m, 1H), 7.80 (t, J=7.9 Hz, 1H), 7.65 (s, 1H), 7.60 (t, J=7.6 Hz, 1H), 7.37 (d, J=7.6 Hz, 1H), 5.74 (br. s., 1H), 5.51 (br. s., 1H), 5.00 (br. s., 1H), 4.91 - 4.72 (m, J=10.4 Hz, 1H), 4.65 - 4.56 (m, 1H), 4.52 - 4.41 (m, 1H), 3.97 (s, 3H), 3.93 - 3.88 (m, 1H), 3.75 - 3.70 (m, 1H), 3.64 - 3.54 (m, 2H), 3.40 - 3.36 (m, 1H), 3.19 - 3.12 (m, 1H), 2.71 - 2.59 (m, 1H), 2.35 - 2.25 (m, 2H), 1.88 (d, J=13.4 Hz, 2H), 1.68 (br. s., 1H), 1.63 (br. s., 1H), 1.58 - 1.48 (m, 4H), 1.45 (d, J=14.6 Hz, 2H), 1.36 (d, J=8.9 Hz, 2H), 1.24 (d, J=14.0 Hz, 2H), 1.17 (br. s., 2H), 1.05 (s, 3H), 0.94 (d, J=6.7 Hz, 3H), 0.91 (d, J=6.1 Hz, 3H), 0.84 (s, 1H), 0.74 (br. s., 1H). MS: MS *m/z* 828.4 (M^++1).

Preparation of Compounds 1057 and 1058



Compound 1057



Compound 1058

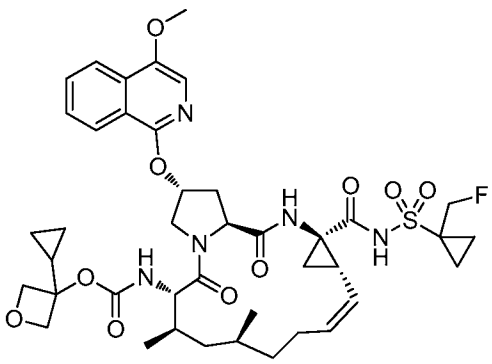
Compounds 1057 and 1058 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1057: 3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-

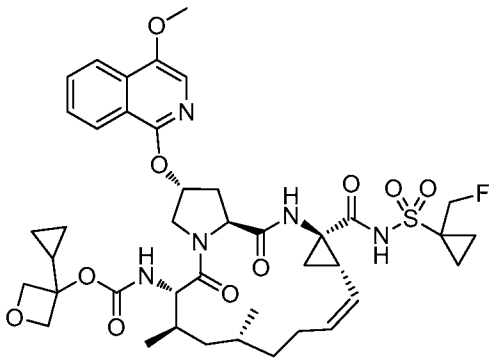
7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 882.4 (M^++1).

Compound 1058: 3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, METHANOL-d4) Shift 8.15 (d, J=8.2 Hz, 1H), 8.09 (d, J=8.2 Hz, 1H), 7.76 - 7.69 (m, 1H), 7.57 - 7.53 (m, 1H), 7.53 (s, 1H), 5.78 (t, J=3.4 Hz, 1H), 5.47 (td, J=10.1, 5.5 Hz, 1H), 5.20 (t, J=9.6 Hz, 1H), 4.85 - 4.71 (m, 1H), 4.65 (dd, J=11.0, 4.0 Hz, 2H), 4.62 - 4.53 (m, 2H), 4.13 (dd, J=11.9, 1.8 Hz, 1H), 4.05 (dd, J=11.4, 3.5 Hz, 1H), 4.01 (s, 3H), 3.94 (d, J=11.0 Hz, 1H), 3.64 (d, J=10.7 Hz, 1H), 3.48 - 3.43 (m, 1H), 3.43 - 3.33 (m, 1H), 2.73 (dd, J=14.0, 7.0 Hz, 1H), 2.59 (q, J=9.2 Hz, 1H), 2.47 - 2.25 (m, 3H), 1.93 - 1.83 (m, 2H), 1.83 - 1.76 (m, 1H), 1.76 - 1.68 (m, 2H), 1.66 (dd, J=8.5, 5.2 Hz, 1H), 1.63 - 1.55 (m, 2H), 1.55 - 1.48 (m, 2H), 1.43 - 1.36 (m, 1H), 1.36 - 1.26 (m, 2H), 1.23 - 1.16 (m, 1H), 1.16 - 1.07 (m, 2H), 1.01 (d, J=6.4 Hz, 3H), 0.98 (d, J=7.0 Hz, 3H), 0.84 - 0.78 (m, 1H). MS: MS *m/z* 882.4 (M^++1).

Preparation of Compounds 1059 and 1060



Compound 1059



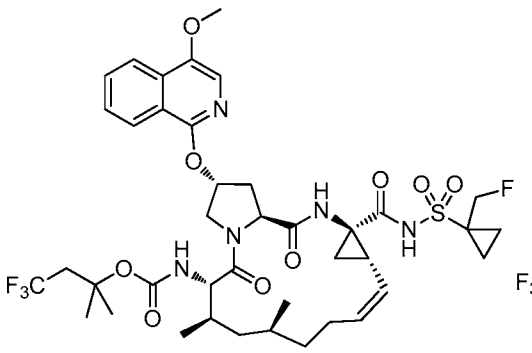
Compound 1060

Compounds 1059 and 1060 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

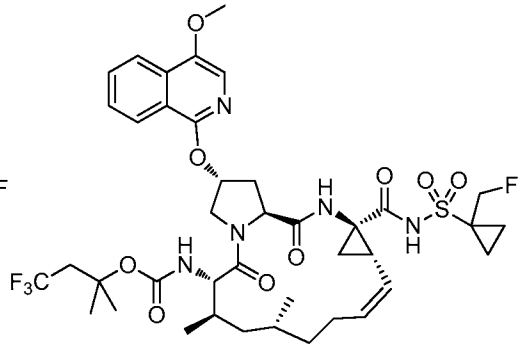
Compound 1059: 3-cyclopropyloxetan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 826.1 (M^++1).

Compound 1060: 3-cyclopropyloxetan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.29 (s, 1H), 9.06 (br. s., 1H), 8.07 (d, J=5.2 Hz, 1H), 8.06 (d, J=4.9 Hz, 1H), 7.80 (t, J=7.5 Hz, 1H), 7.71 (d, J=7.9 Hz, 1H), 7.65 (s, 1H), 7.62 (t, J=7.6 Hz, 1H), 5.74 (br. s., 1H), 5.52 (br. s., 1H), 5.02 - 4.97 (m, 1H), 4.90 - 4.73 (m, J=11.0 Hz, 1H), 4.62 - 4.47 (m, 3H), 4.34 (d, J=7.3 Hz, 1H), 4.07 (d, J=7.6 Hz, 1H), 4.02 (d, J=7.0 Hz, 1H), 3.98 (s, 3H), 3.95 - 3.91 (m, 1H), 3.77 - 3.72 (m, 2H), 2.73 - 2.63 (m, 1H), 2.61 (br. s., 1H), 2.35 - 2.26 (m, 2H), 1.91 (br. s., 1H), 1.84 (br. s., 1H), 1.70 (br. s., 1H), 1.53 (br. s., 4H), 1.43 (br. s., 1H), 1.38 (br. s., 1H), 1.31 - 1.20 (m, 2H), 1.16 (br. s., 1H), 1.01 (dt, J=13.4, 6.9 Hz, 1H), 0.94 (d, J=6.7 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.79 - 0.70 (m, 1H), 0.34 - 0.28 (m, 2H), 0.24 - 0.15 (m, 2H). MS: MS *m/z* 826.1 (M^++1).

Preparation of Compounds 1061 and 1062



Compound 1061



Compound 1062

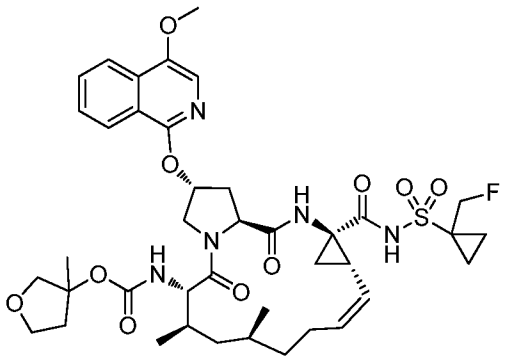
Compounds 1061 and 1062 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1061: 4,4,4-trifluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 854.4 (M^++1).

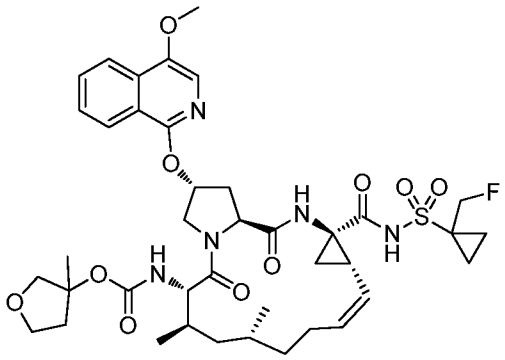
Compound 1062: 4,4,4-trifluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.29 (br. s., 1H), 9.04 (br. s., 1H), 8.07 (d, J=5.2 Hz, 1H), 8.06 (d, J=5.8 Hz, 1H), 7.79 (t, J=8.1 Hz, 1H), 7.70 - 7.65 (m, 1H), 7.60 (t, J=7.6 Hz, 1H), 7.43 (d, J=6.4 Hz, 1H), 5.76 (br. s., 1H), 5.52 (br. s., 1H), 4.99 (br. s., 1H), 4.91 - 4.72 (m, J=9.2 Hz, 1H), 4.58 (br. s., 1H), 4.55 - 4.41 (m, 2H), 3.97 (s, 3H), 3.95 - 3.90 (m, 1H), 3.73 (dd, J=10.7, 8.5 Hz, 1H), 2.74 - 2.62 (m, 2H), 2.62 - 2.54 (m, 1H), 2.34 - 2.25 (m, 2H), 1.89 (br. s., 1H), 1.82 (br. s., 1H), 1.68 (br. s., 1H),

1.53 (br. s., 4H), 1.39 (d, J=16.5 Hz, 3H), 1.26 (br. s., 1H), 1.22 (s, 3H), 1.15 (br. s., 2H), 1.10 - 1.05 (m, 3H), 0.93 (d, J=7.0 Hz, 3H), 0.86 (d, J=6.4 Hz, 3H), 0.73 (br. s., 1H). MS: MS *m/z* 854.4 (M^++1).

Preparation of Compound 1063 and 1064



Compound 1063



Compound 1064

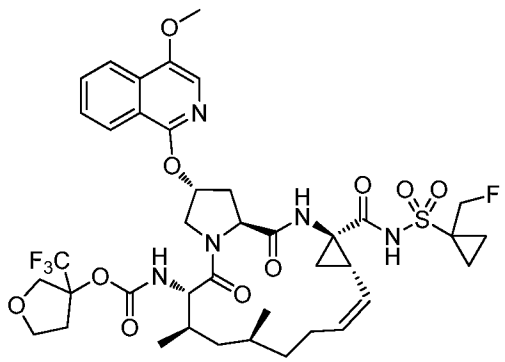
Compounds 1063 and 1064 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1063: 3-methyltetrahydrofuran-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 814.4 (M^++1).

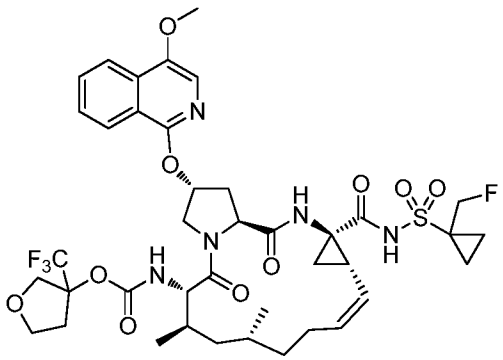
Compound 1064: 3-methyltetrahydrofuran-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (br. s., 1H), 9.01 (br. s., 1H), 8.11 (d, *J*=8.2 Hz, 1H), 8.06 (d, *J*=8.2 Hz, 1H), 7.80 (t, *J*=7.8 Hz, 1H), 7.66 (s, 1H), 7.62 (t, *J*=7.6 Hz, 1H), 7.49 (br. s., 1H), 5.75 (br. s., 1H), 5.52 (br. s., 1H), 5.31 (br. s., 1H), 5.00 (br. s., 1H), 4.89 - 4.73 (m, 1H), 4.60 (br. s., 1H), 4.46 (br. s., 2H), 3.98 (s, 3H), 3.91

(d, *J*=10.7 Hz, 1H), 3.73 (dd, *J*=10.4, 8.5 Hz, 1H), 3.69 - 3.63 (m, 2H), 3.60 (d, *J*=9.5 Hz, 1H), 3.26 (d, *J*=10.1 Hz, 1H), 2.65 (d, *J*=1.8 Hz, 1H), 2.34 - 2.27 (m, 2H), 2.08 (dt, *J*=12.9, 6.2 Hz, 1H), 1.92 (s, 1H), 1.83 (br. s., 1H), 1.81 - 1.65 (m, 2H), 1.53 (br. s., 2H), 1.38 (br. s., 3H), 1.31 - 1.27 (m, 1H), 1.25 (s, 3H), 1.21 - 1.10 (m, 2H), 0.94 (d, *J*=6.1 Hz, 3H), 0.89 (br. s., 3H), 0.74 (br. s., 1H), 0.69 - 0.60 (m, 1H). MS: MS *m/z* 814.4 (M^++1).

Preparation of Compounds 1065 and 1066



Compound 1065



Compound 1066

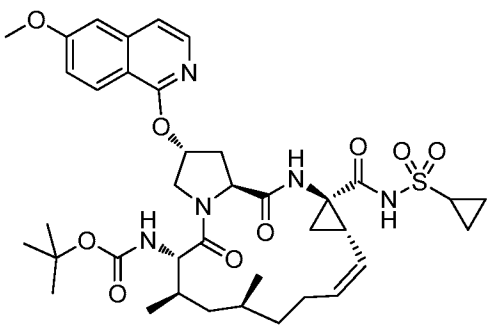
Compounds 1065 and 1066 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1065: 3-(trifluoromethyl)tetrahydrofuran-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 868.4 (M^++1).

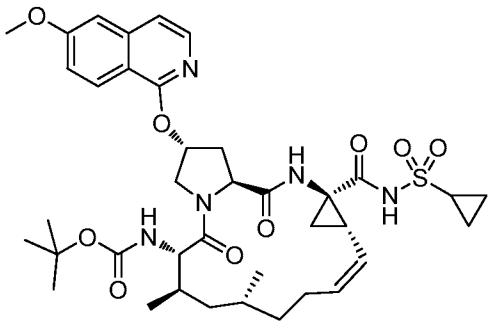
Compound 1066: 3-(trifluoromethyl)tetrahydrofuran-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.27 (br. s., 1H), 9.05 (br. s., 1H), 8.13 - 8.02 (m, 3H), 7.84 - 7.78 (m, 1H), 7.66 (d, J=2.1 Hz, 1H), 7.65 - 7.61 (m, 1H), 5.78 (d, J=15.9 Hz, 1H), 5.52 (br. s., 1H), 5.00 (br. s., 1H), 4.88 - 4.73 (m, J=11.3 Hz, 1H), 4.50 (d, J=9.5 Hz, 3H), 3.98 (d, J=2.4 Hz, 3H), 3.97 - 3.80 (m, 3H), 3.79 - 3.71 (m, 2H), 3.70 - 3.53 (m, 2H), 2.66 (d, J=9.8 Hz, 1H), 2.36 - 2.25 (m, 2H), 2.15 - 2.07 (m, 1H), 1.93 - 1.83 (m, 3H), 1.77 (br. s., 1H), 1.70 (br. s., 1H), 1.53 (br. s., 3H), 1.43 (br. s., 1H), 1.37 (br. s., 1H), 1.32 - 1.20 (m, 2H), 1.20 - 1.11 (m, 1H), 0.94 (d, J=5.2 Hz, 3H), 0.89 (dd, J=13.0, 6.3 Hz, 3H), 0.76 (br. s., 1H). MS: MS *m/z* 868.4 (M^++1).

Preparation of Compounds 1067 and 1068



Compound 1067



Compound 1068

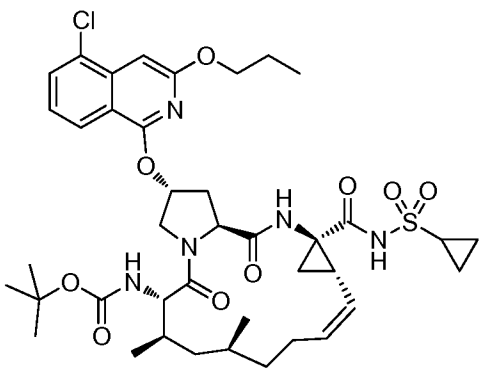
Compounds 1067 and 1068 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1067: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 754.4 (M^++1).

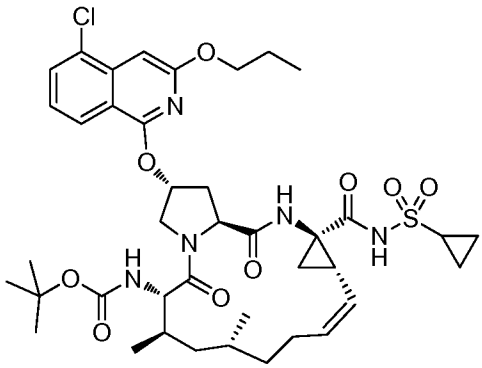
Compound 1068: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500 MHz, CHLOROFORM-d) d ppm 0.72 - 0.83 (m, 2 H) 0.88 - 0.94 (m, 1 H) 0.99 (d, J=7.02 Hz, 6 H) 1.05 - 1.13 (m, 2 H) 1.15 (d, J=10.07 Hz, 2 H) 1.20 (s, 9 H) 1.35 - 1.40 (m, 2 H) 1.40 - 1.48 (m, 2 H) 1.48 - 1.51 (m, 1 H) 1.64 - 1.72 (m, 1 H) 1.72 - 1.86 (m, 1 H) 1.92 - 1.99 (m, 2 H) 2.21 - 2.36 (m, 1 H) 2.44 - 2.56 (m, 1 H) 2.66 - 2.78 (m, 1 H) 2.86 - 2.97 (m, 1 H) 3.92 (s, 3 H) 3.99 - 4.09 (m, 1 H) 4.38 - 4.46 (m, 1 H) 4.71 (d, J=10.68 Hz, 1 H) 4.93 (t, J=9.92 Hz, 1 H) 5.51 - 5.65 (m, 1 H) 5.87 - 6.00 (m, 1 H) 7.01 (s, 1 H) 7.05 (d, J=8.55 Hz, 1 H) 7.16 (d, J=5.19 Hz, 1 H) 7.93 (d, J=5.80 Hz, 1 H) 8.03 (d, J=8.85 Hz, 1 H) 10.42 (s, 1 H). MS: MS *m/z* 754.4 (M^++1).

Preparation of Compounds 1069 and 1070



Compound 1069



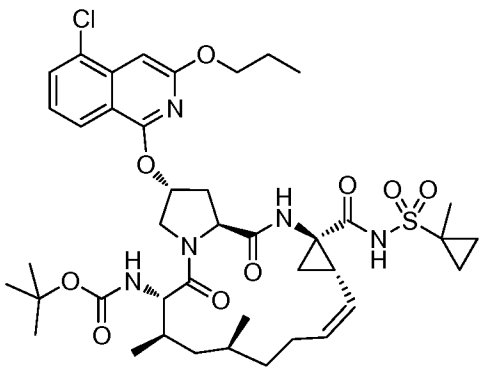
Compound 1070

Compounds 1069 and 1070 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

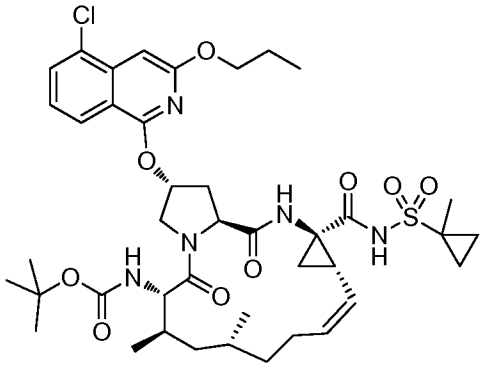
Compound 1069: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 816.7 (M^++1).

Compound 1070: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.21 (br. s., 1H), 8.99 (br. s., 1H), 8.02 (d, J=8.2 Hz, 1H), 7.82 (d, J=7.3 Hz, 1H), 7.27 (t, J=7.8 Hz, 1H), 7.17 (br. s., 1H), 6.80 - 6.74 (m, 1H), 5.79 (br. s., 1H), 5.52 (br. s., 1H), 5.05 (br. s., 1H), 4.65 (br. s., 1H), 4.46 (br. s., 1H), 4.33 - 4.22 (m, 2H), 3.94 - 3.89 (m, 1H), 3.72 - 3.66 (m, 1H), 2.65 (br. s., 2H), 2.39 - 2.23 (m, 2H), 1.91 (d, J=9.5 Hz, 1H), 1.86 - 1.78 (m, 3H), 1.71 (br. s., 1H), 1.59 (br. s., 2H), 1.42 (br. s., 1H), 1.36 (br. s., 1H), 1.22 (br. s., 3H), 1.09 (s, 9H), 1.03 (t, J=7.5 Hz, 4H), 0.99 - 0.96 (m, 1H), 0.93 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.1 Hz, 3H), 0.71 (br. s., 1H). MS: MS *m/z* 816.7 (M^++1).

Preparation of Compounds 1071 and 1072



Compound 1071



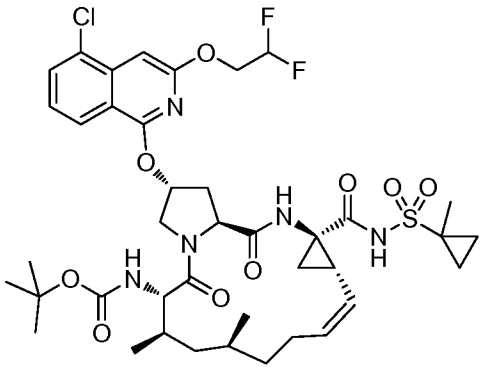
Compound 1072

Compounds 1071 and 1072 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

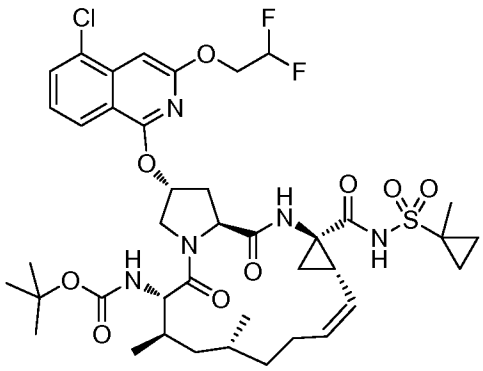
Compound 1071: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 830.7 (M^++1).

Compound 1072: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.06 (s, 1H), 9.12 (br. s., 1H), 8.02 (d, J=8.2 Hz, 1H), 7.88 - 7.80 (m, 1H), 7.27 (t, J=7.9 Hz, 1H), 7.19 (d, J=7.9 Hz, 1H), 6.77 - 6.73 (m, 1H), 5.81 (br. s., 1H), 5.54 (d, J=6.1 Hz, 1H), 4.97 (t, J=9.8 Hz, 1H), 4.68 (d, J=11.0 Hz, 1H), 4.54 - 4.45 (m, 1H), 4.32 - 4.23 (m, 2H), 3.96 - 3.91 (m, 1H), 3.68 (dd, J=10.4, 8.2 Hz, 1H), 2.75 - 2.62 (m, 2H), 2.40 - 2.28 (m, 2H), 1.96 - 1.86 (m, 1H), 1.82 (dq, J=14.2, 7.0 Hz, 3H), 1.74 - 1.66 (m, 1H), 1.62 (br. s., 1H), 1.53 (d, J=9.2 Hz, 1H), 1.46 (d, J=10.7 Hz, 2H), 1.43 - 1.39 (m, 2H), 1.36 (br. s., 1H), 1.29 (d, J=9.8 Hz, 1H), 1.13 (d, J=11.9 Hz, 1H), 1.08 (s, 9H), 1.06 - 1.01 (m, 4H), 0.93 (d, J=7.0 Hz, 3H), 0.91 - 0.86 (m, J=6.4 Hz, 5H), 0.74 (t, J=12.2 Hz, 1H). MS: MS *m/z* 830.7 (M^++1).

Preparation of Compounds 1073 and 1074



Compound 1073



Compound 1074

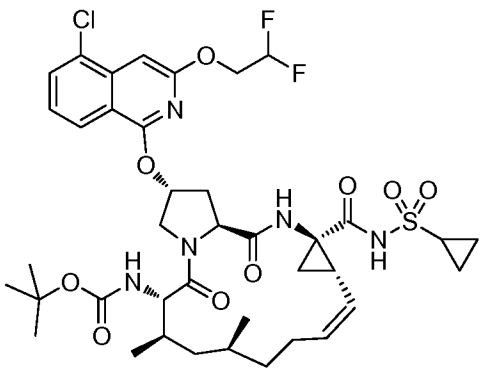
Compounds 1073 and 1074 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1073: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

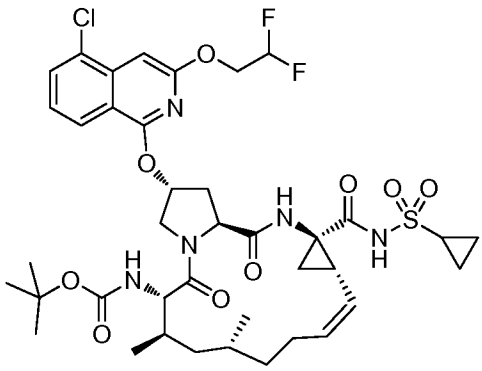
1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 852.8 (M^++1).

Compound 1074: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.07 (br. s., 1H), 9.14 (br. s., 1H), 8.10 - 8.03 (m, 1H), 7.86 (d, J=7.3 Hz, 1H), 7.33 (t, J=7.9 Hz, 1H), 7.19 (br. s., 1H), 6.88 (s, 1H), 6.64 - 6.31 (m, 1H), 5.84 (br. s., 1H), 5.52 (br. s., 1H), 4.97 (br. s., 1H), 4.69 (td, J=14.9, 3.5 Hz, 3H), 4.50 (br. s., 1H), 3.93 (dd, J=11.7, 2.9 Hz, 1H), 3.72 - 3.66 (m, 1H), 2.65 (br. s., 2H), 2.39 - 2.25 (m, 2H), 1.91 (d, J=14.0 Hz, 1H), 1.81 (br. s., 1H), 1.71 (br. s., 1H), 1.61 (br. s., 1H), 1.40 (br. s., 4H), 1.25 (br. s., 3H), 1.19 (br. s., 2H), 1.07 (s, 9H), 1.05 (br. s., 2H), 0.93 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.4 Hz, 3H), 0.73 (br. s., 1H). MS: MS *m/z* 852.8 (M^++1).

Preparation of Compounds 1075 and 1076



Compound 1075



Compound 1076

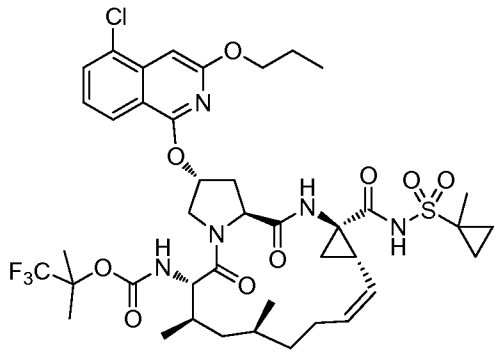
Compounds 1075 and 1076 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1075: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-

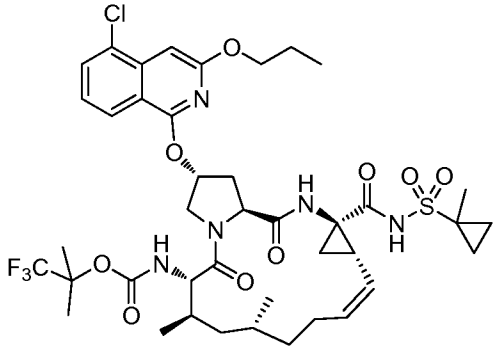
dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 836.6 (M^+-1).

Compound 1076: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.22 (br. s., 1H), 9.02 (br. s., 1H), 8.05 (d, J=8.5 Hz, 1H), 7.86 (d, J=7.6 Hz, 1H), 7.33 (t, J=7.9 Hz, 1H), 7.19 (d, J=6.4 Hz, 1H), 6.88 (s, 1H), 6.65 - 6.34 (m, 1H), 5.83 (br. s., 1H), 5.53 (br. s., 1H), 5.04 (br. s., 1H), 4.75 - 4.64 (m, 3H), 4.49 (br. s., 1H), 3.94 - 3.89 (m, 1H), 3.72 - 3.66 (m, 1H), 2.68 (br. s., 2H), 2.39 - 2.24 (m, 2H), 1.92 (d, J=4.9 Hz, 1H), 1.81 (d, J=6.1 Hz, 1H), 1.70 (br. s., 1H), 1.61 (br. s., 1H), 1.56 (br. s., 1H), 1.43 (br. s., 1H), 1.37 (br. s., 1H), 1.19 (br. s., 1H), 1.13 (br. s., 2H), 1.07 (s, 9H), 1.01 (br. s., 3H), 0.94 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.4 Hz, 3H), 0.74 (d, J=12.8 Hz, 1H). MS: MS *m/z* 836.6 (M^+-1).

Preparation of Compounds 1077 and 1078



Compound 1077



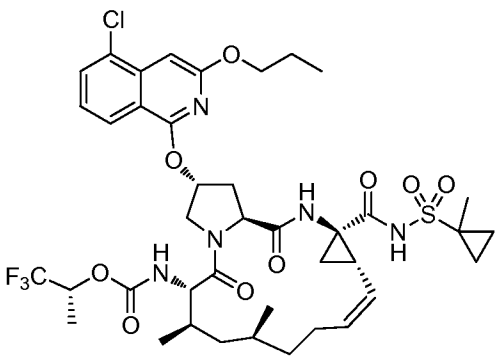
Compound 1078

Compounds 1077 and 1078 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

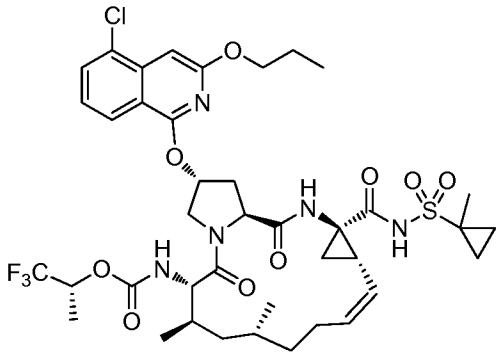
Compound 1077: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 884.66 (M^++1).

Compound 1078: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.05 (br. s., 1H), 9.15 (br. s., 1H), 8.00 (d, J=8.2 Hz, 1H), 7.83 (d, J=7.3 Hz, 2H), 7.31 (t, J=7.9 Hz, 1H), 6.77 (s, 1H), 5.81 (br. s., 1H), 5.53 (br. s., 1H), 4.98 (br. s., 1H), 4.61 (d, J=11.3 Hz, 1H), 4.54 (br. s., 1H), 4.32 - 4.23 (m, 2H), 3.97 - 3.91 (m, 1H), 3.67 (dd, J=10.8, 8.1 Hz, 1H), 2.73 - 2.68 (m, 1H), 2.66 (br. s., 1H), 2.39 - 2.26 (m, 2H), 1.94 - 1.77 (m, 4H), 1.70 (br. s., 1H), 1.62 (br. s., 1H), 1.52 (d, J=16.2 Hz, 1H), 1.49 - 1.38 (m, 5H), 1.35 (br. s., 1H), 1.31 (s, 3H), 1.29 - 1.23 (m, 1H), 1.17 (d, J=8.5 Hz, 1H), 1.03 (t, J=7.3 Hz, 3H), 1.00 (s, 3H), 0.93 (d, J=7.0 Hz, 4H), 0.89 (d, J=6.1 Hz, 3H), 0.75 (t, J=12.4 Hz, 1H). MS: MS *m/z* 884.66 (M^++1).

Preparation of Compounds 1079 and 1080



Compound 1079



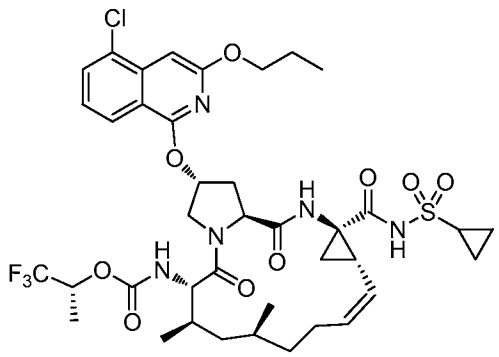
Compound 1080

Compounds 1079 and 1080 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

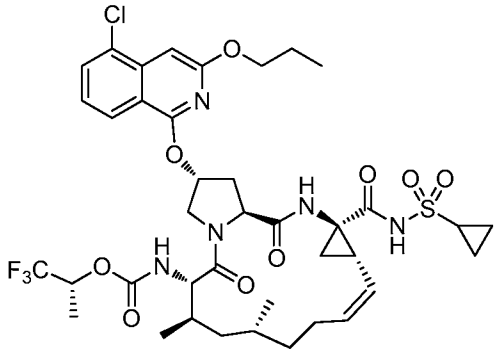
Compound 1079: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 870.62 (M^++1).

Compound 1080: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.04 (br. s., 1H), 9.10 (br. s., 1H), 8.08 (d, J=7.6 Hz, 1H), 7.97 (d, J=8.2 Hz, 1H), 7.87 - 7.81 (m, 1H), 7.25 (t, J=7.9 Hz, 1H), 6.80 - 6.76 (m, 1H), 5.83 (br. s., 1H), 5.51 (br. s., 1H), 5.01 (br. s., 1H), 4.57 (d, J=6.1 Hz, 2H), 4.52 - 4.44 (m, 1H), 4.27 (t, J=6.7 Hz, 2H), 3.96 (dd, J=11.4, 3.2 Hz, 1H), 3.76 (dd, J=10.4, 8.2 Hz, 1H), 2.65 (br. s., 2H), 2.40 - 2.24 (m, 2H), 1.93 - 1.78 (m, 5H), 1.70 (br. s., 1H), 1.59 (br. s., 1H), 1.50 (br. s., 1H), 1.40 (br. s., 4H), 1.37 (d, J=6.4 Hz, 2H), 1.26 (br. s., 1H), 1.17 (d, J=6.7 Hz, 3H), 1.15 - 1.10 (m, 1H), 1.03 (t, J=7.3 Hz, 3H), 0.93 (d, J=6.7 Hz, 3H), 0.90 (d, J=6.4 Hz, 4H), 0.75 (d, J=6.7 Hz, 1H). MS: MS *m/z* 870.62 (M^++1).

Preparation of Compounds 1081 and 1082



Compound 1081



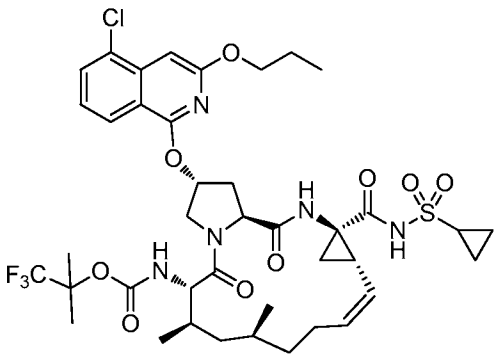
Compound 1082

Compounds 1081 and 1082 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

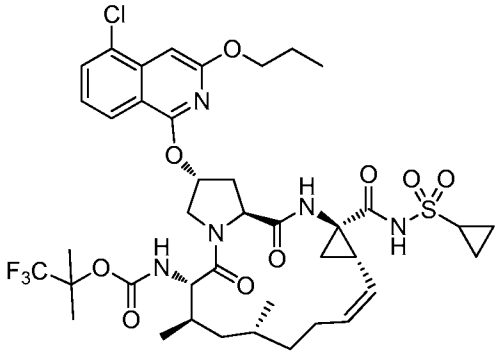
Compound 1081: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 856.7 (M^++1).

Compound 1082: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.18 (s, 1H), 8.98 (br. s., 1H), 8.08 (d, J=7.9 Hz, 1H), 8.00 - 7.95 (m, 1H), 7.86 - 7.81 (m, 1H), 7.25 (t, J=7.8 Hz, 1H), 6.80 - 6.76 (m, 1H), 5.82 (br. s., 1H), 5.52 (br. s., 1H), 5.07 (t, J=9.0 Hz, 1H), 4.64 - 4.52 (m, 2H), 4.52 - 4.44 (m, 1H), 4.27 (t, J=6.6 Hz, 2H), 3.97 - 3.92 (m, 1H), 3.76 (dd, J=10.7, 7.9 Hz, 1H), 2.92 (br. s., 1H), 2.66 (d, J=6.4 Hz, 2H), 2.40 - 2.23 (m, 2H), 1.97 - 1.76 (m, 5H), 1.70 (br. s., 1H), 1.63 - 1.53 (m, 2H), 1.45 (br. s., 1H), 1.37 (br. s., 1H), 1.18 (d, J=6.7 Hz, 3H), 1.13 (br. s., 3H), 1.04 (t, J=7.5 Hz, 4H), 0.94 (d, J=7.0 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.80 - 0.72 (m, 1H). MS: MS *m/z* 856.7 (M^++1).

Preparation of Compounds 1083 and 1084



Compound 1083



Compound 1084

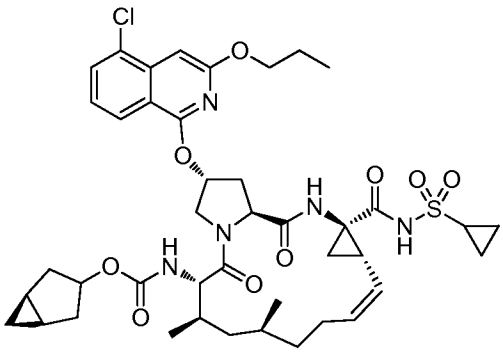
Compounds 1083 and 1084 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1083: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 870.67 (M^++1).

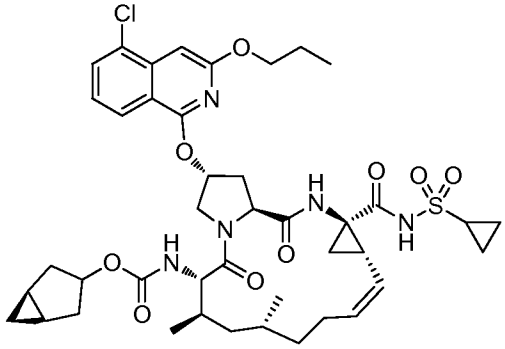
Compound 1084: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.20 (br. s., 1H), 9.03 (br. s., 1H), 8.00 (d, J=8.5 Hz, 1H), 7.83 (d, J=7.6 Hz, 2H), 7.31 (t, J=7.9 Hz, 1H), 6.79 - 6.76 (m, 1H), 5.80 (br. s., 1H), 5.53 (br. s., 1H), 5.06 (br. s., 1H), 4.61 (d, J=11.6 Hz, 1H), 4.54 - 4.48 (m, 1H), 4.33 - 4.22 (m, 2H), 3.95 - 3.89 (m, 1H), 3.67 (dd, J=10.7, 7.9 Hz, 1H), 2.91 (d, J=8.2 Hz, 1H), 2.66 (br. s., 2H), 2.39 - 2.25 (m, 2H), 1.91 (d, J=12.2 Hz, 1H), 1.87 - 1.78 (m, 3H), 1.76 - 1.67 (m, 1H), 1.61 (br. s., 1H), 1.56 (br. s., 1H), 1.42 (br. s., 1H), 1.37 (br. s., 1H), 1.32 (s,

3H), 1.13 (br. s., 3H), 1.05 - 1.01 (m, 6H), 0.98 (br. s., 2H), 0.94 (d, J=6.7 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H), 0.74 (t, J=12.1 Hz, 1H). MS: MS *m/z* 870.67 (M^++1).

Preparation of Compounds 1085 and 1086



Compound 1085



Compound 1086

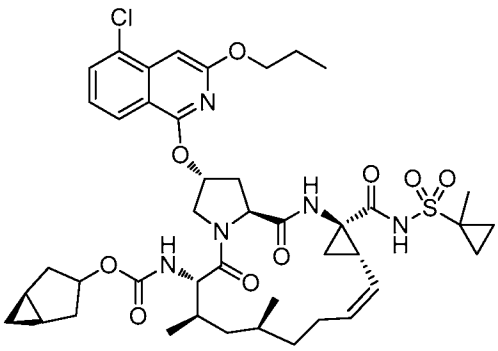
Compounds 1085 and 1086 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1085: (1S,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 840.8 (M^++1).

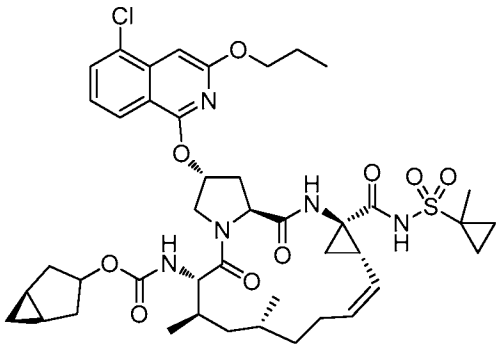
Compound 1086: (1S,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 8.01 (d, J=8.2 Hz, 1H), 7.84 (d, J=7.6 Hz, 1H), 7.39 - 7.29 (m, 2H), 6.77 (s, 1H), 5.80 (br. s., 1H), 5.41 (br. s., 1H), 4.54 (t, J=6.9 Hz, 1H), 4.48 (d, J=9.8 Hz, 1H), 4.42 (br. s., 1H), 4.28 (t, J=6.6 Hz, 2H), 3.97 - 3.91 (m, 1H), 3.77 - 3.71 (m, 1H), 2.56 (br. s., 2H), 2.39 - 2.30 (m, 2H), 2.21 (br. s., 2H), 1.97 - 1.87 (m, 2H), 1.82 (dq, J=14.1, 7.0

Hz, 4H), 1.78 - 1.70 (m, 2H), 1.54 (d, J=14.0 Hz, 2H), 1.50 (br. s., 1H), 1.38 (br. s., 2H), 1.30 (br. s., 2H), 1.24 (d, J=14.0 Hz, 2H), 1.21 - 1.13 (m, 2H), 1.13 - 1.07 (m, 2H), 1.04 (t, J=7.3 Hz, 4H), 0.92 (d, J=6.7 Hz, 3H), 0.85 (d, J=6.4 Hz, 3H), 0.67 (br. s., 1H), 0.35 - 0.28 (m, 2H). MS: MS *m/z* 840.8 (M^++1).

Preparation of Compounds 1087 and 1088



Compound 1087



Compound 1088

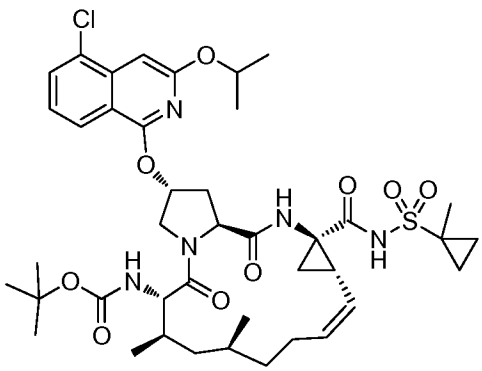
Compounds 1087 and 1088 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1087: (1S,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 854.72 (M^++1).

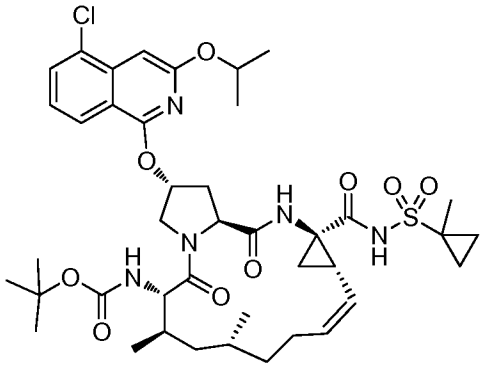
Compound 1088: (1S,5S)-bicyclo[3.1.0]hexan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-propoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.06 (br. s., 1H), 9.08 (br. s., 1H), 8.01 (d, J=8.2 Hz, 1H), 7.85 (d, J=7.3 Hz, 1H), 7.43 - 7.37 (m, 1H), 7.34 - 7.29 (m, 1H), 6.77 (s, 1H), 5.83 (br. s., 1H), 5.51 (br. s.,

1H), 4.58 - 4.45 (m, 3H), 4.27 (t, J=6.6 Hz, 2H), 3.98 - 3.93 (m, 1H), 3.75 - 3.70 (m, 1H), 2.65 (br. s., 1H), 2.39 - 2.24 (m, 2H), 1.97 - 1.88 (m, 2H), 1.82 (dq, J=14.2, 7.0 Hz, 3H), 1.78 - 1.69 (m, 1H), 1.63 (br. s., 2H), 1.55 (d, J=14.3 Hz, 1H), 1.52 - 1.43 (m, 3H), 1.40 (br. s., 4H), 1.37 - 1.27 (m, 3H), 1.24 (d, J=14.3 Hz, 2H), 1.21 - 1.16 (m, 1H), 1.16 - 1.06 (m, 2H), 1.04 (t, J=7.3 Hz, 3H), 0.92 (d, J=6.7 Hz, 3H), 0.90 - 0.88 (m, 1H), 0.86 (d, J=6.4 Hz, 3H), 0.73 (br. s., 1H), 0.35 - 0.29 (m, 2H). MS: MS *m/z* 854.72 (M^++1).

Preparation of Compounds 1089 and 1090



Compound 1089



Compound 1090

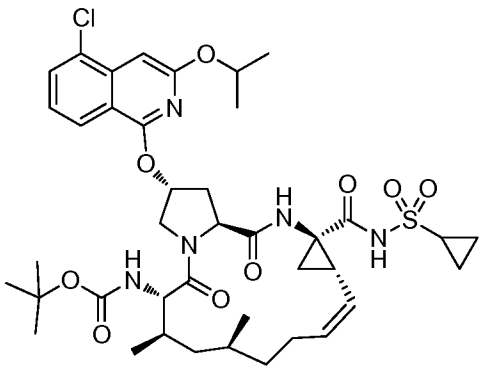
Compounds 1089 and 1090 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1089: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 830.8 (M^++1).

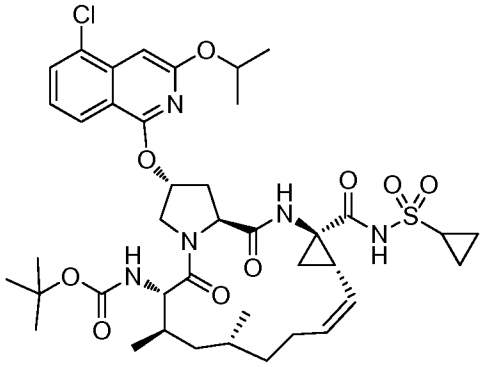
Compound 1090: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-

a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.07 (br. s., 1H), 9.10 (br. s., 1H), 8.02 (d, J=8.2 Hz, 1H), 7.80 (d, J=7.0 Hz, 1H), 7.26 (t, J=7.9 Hz, 1H), 7.17 (br. s., 1H), 6.77 - 6.72 (m, 1H), 5.78 (br. s., 1H), 5.48 (br. s., 1H), 5.23 (dt, J=12.2, 6.1 Hz, 1H), 4.66 (br. s., 1H), 4.48 (br. s., 1H), 3.96 - 3.90 (m, 1H), 3.69 (dd, J=10.2, 8.7 Hz, 1H), 2.65 (br. s., 1H), 2.61 (br. s., 1H), 2.39 - 2.28 (m, 2H), 1.89 (br. s., 1H), 1.81 (d, J=5.2 Hz, 1H), 1.73 (br. s., 1H), 1.56 (br. s., 1H), 1.51 (br. s., 1H), 1.47 - 1.41 (m, 1H), 1.38 (dd, J=6.1, 2.4 Hz, 10H), 1.35 - 1.29 (m, 1H), 1.23 (d, J=17.7 Hz, 3H), 1.08 (s, 9H), 1.06 - 1.02 (m, 1H), 0.93 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.4 Hz, 3H), 0.70 (br. s., 1H). MS: MS *m/z* 830.8 (M^++1).

Preparation of Compounds 1091 and 1092



Compound 1091



Compound 1092

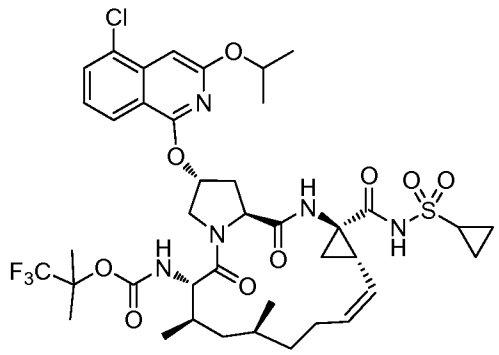
Compounds 1091 and 1092 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1091: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-isopropoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 816.74 (M^++1).

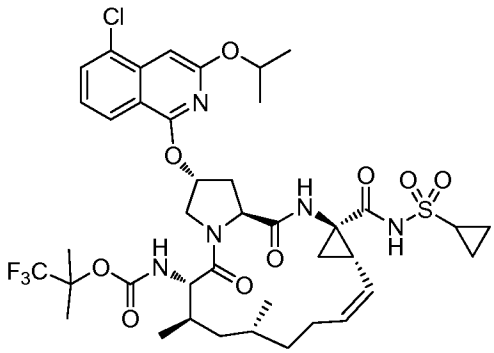
Compound 1092: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-isopropoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-

dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.23 (br. s., 1H), 8.99 (br. s., 1H), 8.02 (d, J=8.2 Hz, 1H), 7.81 (d, J=7.3 Hz, 1H), 7.26 (t, J=7.9 Hz, 1H), 7.18 (br. s., 1H), 6.73 (s, 1H), 5.78 (br. s., 1H), 5.51 (br. s., 1H), 5.23 (dt, J=12.0, 6.1 Hz, 1H), 5.05 (br. s., 1H), 4.66 (br. s., 1H), 4.46 (br. s., 1H), 3.94 - 3.89 (m, 1H), 3.71 - 3.66 (m, 1H), 2.65 (br. s., 2H), 2.39 - 2.29 (m, 2H), 1.91 (br. s., 1H), 1.81 (d, J=5.5 Hz, 1H), 1.70 (br. s., 1H), 1.59 (br. s., 1H), 1.51 (d, J=6.1 Hz, 1H), 1.38 (d, J=6.1 Hz, 7H), 1.36 - 1.30 (m, 1H), 1.23 (d, J=18.9 Hz, 1H), 1.20 - 1.12 (m, 2H), 1.09 (s, 9H), 1.04 (br. s., 3H), 0.93 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.4 Hz, 3H), 0.71 (br. s., 1H). MS: MS *m/z* 816.74 (M^++1).

Preparation of Compounds 1093 and 1094



Compound 1093



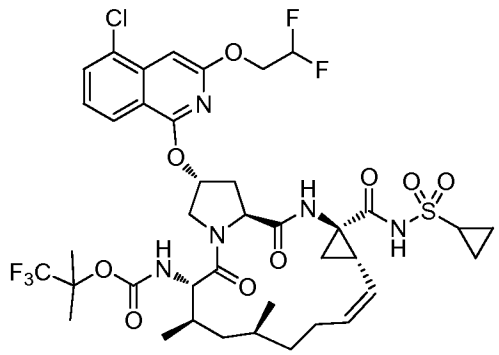
Compound 1094

Compounds 1093 and 1094 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

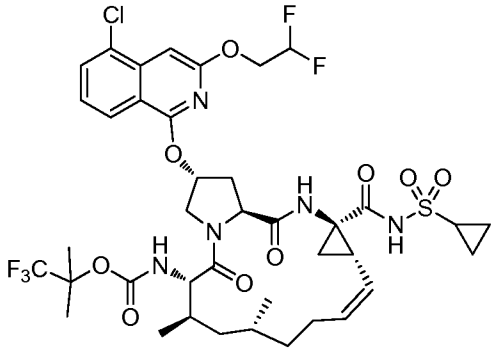
Compound 1093: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-isopropoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 870.46 (M^++1).

Compound 1094: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-isopropoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.21 (br. s., 1H), 9.03 (br. s., 1H), 7.99 (d, J=8.2 Hz, 1H), 7.87 - 7.80 (m, 2H), 7.30 (t, J=7.9 Hz, 1H), 6.74 (s, 1H), 5.80 (br. s., 1H), 5.53 (br. s., 1H), 5.23 (dt, J=12.2, 6.1 Hz, 1H), 5.06 (br. s., 1H), 4.62 (d, J=11.3 Hz, 1H), 4.52 (t, J=8.4 Hz, 1H), 3.95 - 3.90 (m, 1H), 3.67 (dd, J=10.7, 7.9 Hz, 1H), 2.96 - 2.88 (m, 1H), 2.65 (br. s., 1H), 2.39 - 2.24 (m, 2H), 1.95 - 1.79 (m, 2H), 1.71 (br. s., 1H), 1.62 (br. s., 1H), 1.57 (br. s., 1H), 1.43 (br. s., 1H), 1.38 (dd, J=6.1, 2.4 Hz, 7H), 1.33 (s, 3H), 1.25 (br. s., 1H), 1.20 (br. s., 1H), 1.14 (br. s., 2H), 1.03 (br. s., 1H), 1.01 (s, 4H), 0.94 (d, J=7.0 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H), 0.74 (t, J=12.1 Hz, 1H). MS: MS *m/z* 870.46 (M^++1).

Preparation of Compounds 1095 and 1096



Compound 1095



Compound 1096

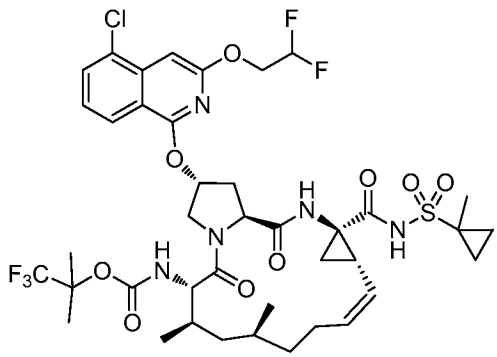
Compounds 1095 and 1096 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1095: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-

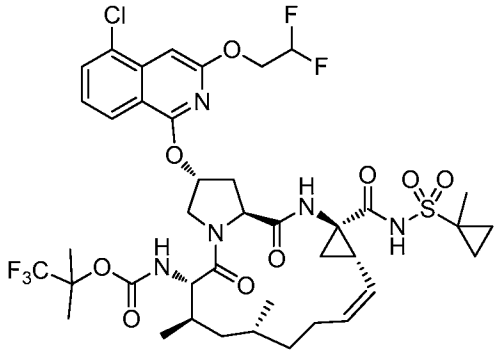
1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 892.43 (M^++1).

Compound 1096: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.21 (br. s., 1H), 9.05 (br. s., 1H), 8.03 (d, J=8.2 Hz, 1H), 7.88 (d, J=7.6 Hz, 1H), 7.84 (d, J=7.6 Hz, 1H), 7.37 (t, J=7.9 Hz, 1H), 6.89 (s, 1H), 6.63 - 6.36 (m, 1H), 5.85 (br. s., 1H), 5.53 (br. s., 1H), 5.05 (br. s., 1H), 4.73 - 4.60 (m, 3H), 4.55 - 4.49 (m, 1H), 3.94 - 3.89 (m, 1H), 3.68 (dd, J=10.7, 7.9 Hz, 1H), 2.91 (d, J=8.9 Hz, 1H), 2.67 (br. s., 2H), 2.40 - 2.25 (m, 2H), 1.95 - 1.79 (m, 2H), 1.70 (br. s., 1H), 1.62 (br. s., 1H), 1.57 (br. s., 1H), 1.44 (br. s., 1H), 1.38 (d, J=13.4 Hz, 1H), 1.31 (s, 3H), 1.14 (br. s., 3H), 1.01 (s, 3H), 0.99 - 0.96 (m, 2H), 0.94 (d, J=7.0 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H), 0.75 (t, J=12.1 Hz, 1H). MS: MS *m/z* 892.43 (M^++1).

Preparation of Compounds 1097 and 1098



Compound 1097



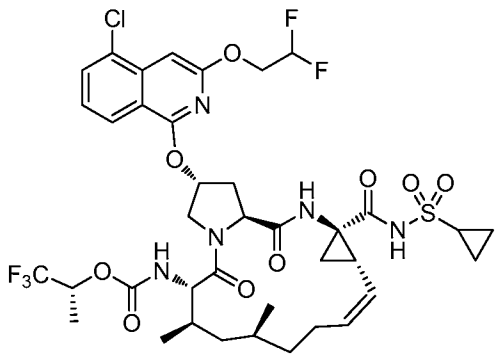
Compound 1098

Compounds 1097 and 1098 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

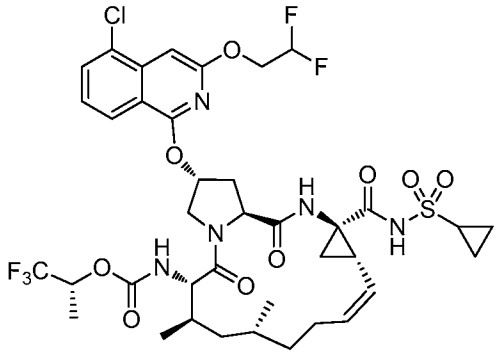
Compound 1097: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 904.5 (M^+-1).

Compound 1098: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.06 (br. s., 1H), 9.19 (br. s., 1H), 8.07 - 8.01 (m, 1H), 7.94 - 7.82 (m, 2H), 7.37 (t, J=7.9 Hz, 1H), 6.89 (s, 1H), 6.65 - 6.29 (m, 1H), 5.86 (br. s., 1H), 5.54 (d, J=6.1 Hz, 1H), 4.98 (d, J=8.9 Hz, 1H), 4.77 - 4.61 (m, 3H), 4.61 - 4.52 (m, 1H), 3.97 - 3.91 (m, 1H), 3.69 (dd, J=10.7, 7.9 Hz, 1H), 2.73 - 2.62 (m, 2H), 2.39 - 2.27 (m, 2H), 1.94 - 1.79 (m, 2H), 1.74 - 1.66 (m, 1H), 1.63 (br. s., 1H), 1.54 (br. s., 1H), 1.50 (br. s., 2H), 1.44 - 1.40 (m, 4H), 1.35 (d, J=12.8 Hz, 1H), 1.30 (s, 4H), 1.14 (d, J=13.4 Hz, 1H), 1.02 - 0.97 (m, 3H), 0.93 (d, J=7.0 Hz, 3H), 0.89 (d, J=6.1 Hz, 4H), 0.76 (t, J=12.2 Hz, 1H). MS: MS *m/z* 904.5 (M^+-1).

Preparation of Compounds 1099 and 1100



Compound 1099



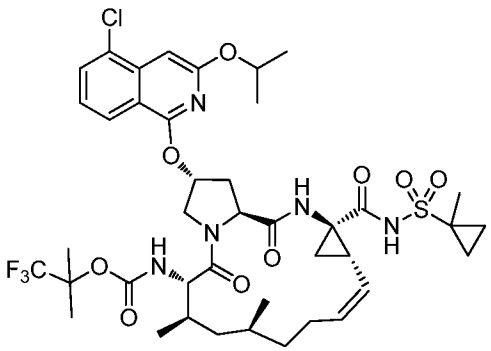
Compound 1100

Compounds 1099 and 1100 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

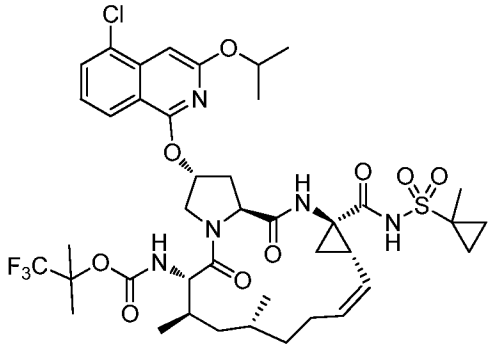
Compound 1099: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 878.37 (M^++1).

Compound 1100: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.20 (s, 1H), 9.01 (br. s., 1H), 8.09 (d, J=7.9 Hz, 1H), 8.04 - 7.96 (m, 1H), 7.90 - 7.85 (m, 1H), 7.31 (t, J=7.9 Hz, 1H), 6.89 (s, 1H), 6.63 - 6.34 (m, 1H), 5.86 (br. s., 1H), 5.54 (d, J=6.4 Hz, 1H), 5.06 (t, J=9.6 Hz, 1H), 4.69 (tt, J=15.0, 3.7 Hz, 2H), 4.61 (d, J=11.9 Hz, 1H), 4.58 - 4.52 (m, 1H), 4.52 - 4.46 (m, 1H), 3.96 - 3.91 (m, 1H), 3.76 (dd, J=10.5, 8.1 Hz, 1H), 2.96 - 2.89 (m, 1H), 2.66 (d, J=8.9 Hz, 2H), 2.39 - 2.31 (m, 1H), 2.27 (d, J=11.0 Hz, 1H), 1.98 - 1.82 (m, 2H), 1.68 (br. s., 1H), 1.61 (br. s., 1H), 1.56 (br. s., 1H), 1.45 (br. s., 1H), 1.37 (br. s., 1H), 1.17 (d, J=6.7 Hz, 3H), 1.13 (br. s., 3H), 1.06 - 0.95 (m, 2H), 0.94 (d, J=6.7 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.76 (t, J=12.1 Hz, 1H). MS: MS *m/z* 878.37 (M^++1).

Preparation of Compounds 1101 and 1102



Compound 1101



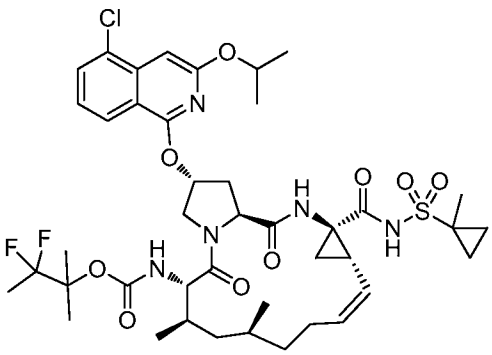
Compound 1102

Compounds 1101 and 1102 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

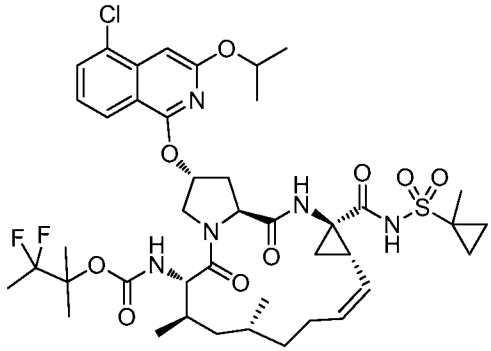
Compound 1101: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 884.5 (M^++1).

Compound 1102: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.07 (br. s., 1H), 9.15 (br. s., 1H), 8.02 - 7.96 (m, 1H), 7.82 (d, J=7.0 Hz, 2H), 7.29 (t, J=7.9 Hz, 1H), 6.74 (s, 1H), 5.80 (br. s., 1H), 5.52 (br. s., 1H), 5.23 (dt, J=12.1, 5.9 Hz, 1H), 4.99 (br. s., 1H), 4.61 (br. s., 1H), 4.53 (br. s., 1H), 3.96 - 3.91 (m, 1H), 3.67 (dd, J=10.4, 7.9 Hz, 1H), 2.65 (br. s., 1H), 2.39 - 2.25 (m, 2H), 1.92 (s, 1H), 1.84 (br. s., 2H), 1.71 (br. s., 1H), 1.60 (br. s., 1H), 1.50 (br. s., 2H), 1.38 (d, J=6.1 Hz, 10H), 1.33 (br. s., 4H), 1.25 (br. s., 2H), 1.20 (br. s., 2H), 1.00 (br. s., 3H), 0.93 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.4 Hz, 3H), 0.73 (br. s., 1H). MS: MS *m/z* 884.5 (M^++1).

Preparation of Compounds 1103 and 1104



Compound 1103



Compound 1104

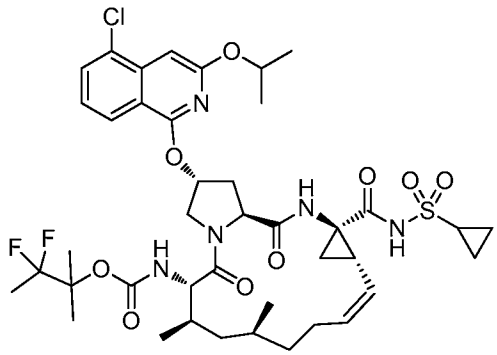
Compounds 1103 and 1104 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compou nd 1103: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 880.6 (M^++1).

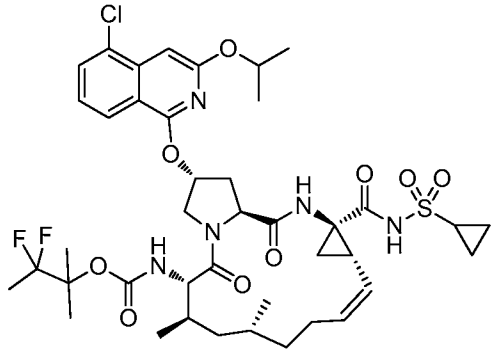
Compound 1104: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.07 (br. s., 1H), 9.13 (br. s., 1H), 8.00 (d, J=8.2 Hz, 1H), 7.82 (d, J=7.3 Hz, 1H), 7.62 (d, J=7.6 Hz, 1H), 7.28 (t, J=7.8 Hz, 1H), 6.74 (s, 1H), 5.80 (br. s., 1H), 5.53 (br. s., 1H), 5.23 (dt, J=12.2, 6.1 Hz, 1H), 4.98 (br. s., 1H), 4.64 (d, J=10.7 Hz, 1H), 4.54 (br. s., 1H), 3.95 (dd, J=11.6, 3.1 Hz, 1H), 3.68 (dd, J=10.7, 8.2 Hz, 1H), 2.65 (br. s., 1H), 2.39 - 2.28 (m, 2H), 1.92 (d, J=8.9 Hz, 1H), 1.83 (d, J=6.4 Hz, 1H), 1.68 (br. s., 1H), 1.62 (br. s., 1H), 1.59 (s, 1H), 1.56 (s, 2H), 1.52 (s, 2H), 1.45 (d, J=7.3 Hz, 2H), 1.41 (br. s., 4H), 1.40 - 1.35 (m, 9H), 1.26 (d, J=14.0 Hz, 3H), 1.23 (s, 3H), 1.15 (d,

J=6.7 Hz, 1H), 0.94 (d, J=6.7 Hz, 3H), 0.92 - 0.88 (m, 3H), 0.76 (t, J=11.7 Hz, 1H). MS: MS *m/z* 880.6 (M^++1).

Preparation of Compounds 1105 and 1106



Compound 1105



Compound 1106

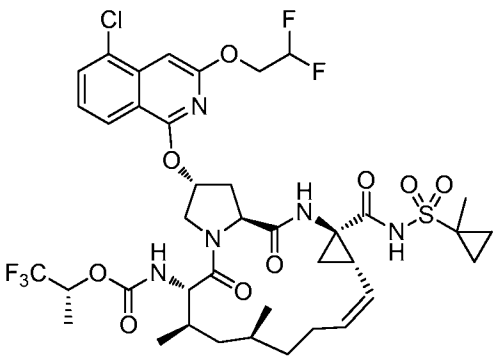
Compounds 1105 and 1106 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1105: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-isopropoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 866.6 (M^++1).

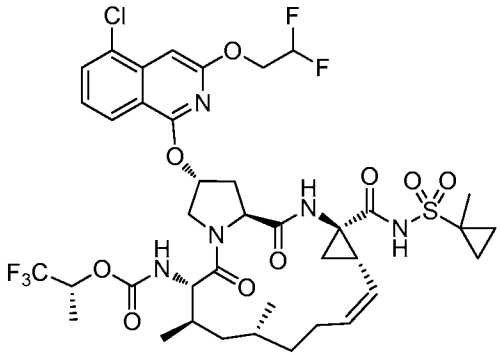
Compound 1106: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-isopropoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.22 (br. s., 1H), 9.01 (br. s., 1H), 8.02 - 7.96 (m, 1H), 7.82 (d, J=7.3 Hz, 1H), 7.61 (d, J=7.3 Hz, 1H), 7.28 (t, J=7.9 Hz, 1H), 6.74 (s, 1H), 5.79 (br. s., 1H), 5.52 (br. s., 1H), 5.23 (dt, J=12.1, 6.0 Hz, 1H), 5.06 (br. s., 1H), 4.63 (d, J=9.5 Hz, 1H), 4.50 (br. s., 1H), 3.95 - 3.90 (m, 1H), 3.68 (dd, J=10.7, 8.2 Hz, 1H), 2.65 (br. s., 2H), 2.40 -

2.22 (m, 2H), 1.96 - 1.87 (m, 1H), 1.82 (d, J=7.0 Hz, 1H), 1.71 (br. s., 1H), 1.56 (t, J=19.5 Hz, 4H), 1.49 (br. s., 1H), 1.43 (br. s., 1H), 1.38 (dd, J=6.1, 1.2 Hz, 7H), 1.24 (s, 3H), 1.13 (br. s., 3H), 1.07 - 0.96 (m, 2H), 0.96 - 0.91 (m, 6H), 0.89 (d, J=6.4 Hz, 4H), 0.74 (br. s., 1H). MS: MS *m/z* 866.6 (M^++1).

Preparation of Compounds 1107 and 1108



Compound 1107



Compound 1108

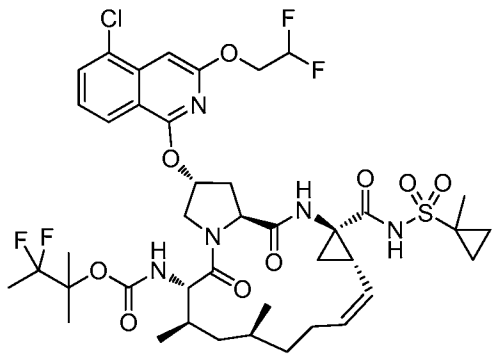
Compounds 1107 and 1108 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1107: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 892.5 (M^++1).

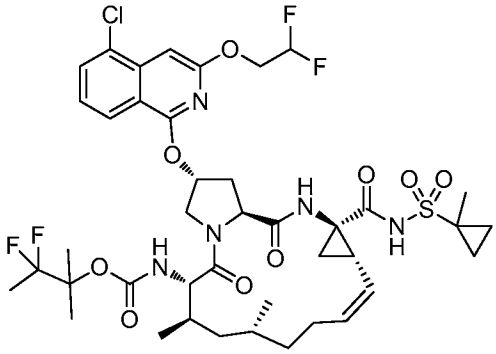
Compound 1108: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.06 (br. s., 1H), 9.13 (br. s., 1H), 8.09 (d, J=7.9 Hz, 1H), 8.03 - 7.98 (m, 1H), 7.90 - 7.85 (m, 1H), 7.31 (t, J=7.9 Hz, 1H), 6.89 (s, 1H), 6.65 - 6.27 (m, 1H), 5.87 (br. s.,

1H), 5.53 (br. s., 1H), 4.98 (br. s., 1H), 4.73 - 4.64 (m, 2H), 4.64 - 4.58 (m, 1H), 4.53 (d, J=7.0 Hz, 2H), 3.96 (d, J=8.5 Hz, 1H), 3.76 (dd, J=10.7, 7.9 Hz, 1H), 2.67 (br. s., 2H), 2.39 - 2.27 (m, 2H), 1.92 (s, 1H), 1.87 (d, J=7.3 Hz, 1H), 1.67 (br. s., 1H), 1.62 (br. s., 1H), 1.52 (br. s., 1H), 1.48 - 1.43 (m, 2H), 1.41 (br. s., 3H), 1.34 (d, J=16.8 Hz, 3H), 1.28 (br. s., 1H), 1.25 (s, 1H), 1.16 (d, J=6.4 Hz, 3H), 0.93 (d, J=7.0 Hz, 3H), 0.91 - 0.89 (m, J=6.1 Hz, 3H), 0.79 (d, J=11.9 Hz, 1H). MS: MS *m/z* 892.5 (M^++1).

Preparation of Compounds 1109 and 1110



Compound 1109



Compound 1110

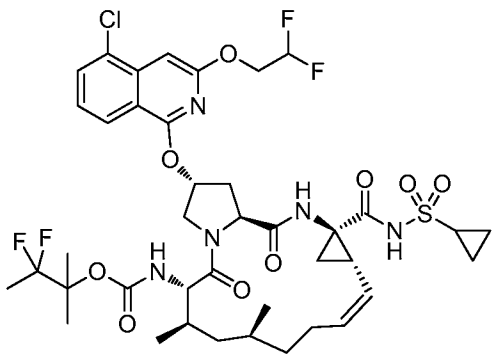
Compounds 1109 and 1110 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1109: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 903.4 (M^++1).

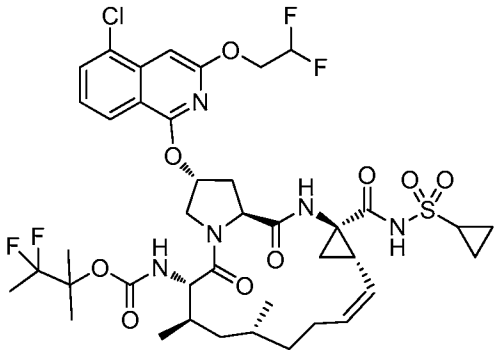
Compound 1110: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-

a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.06 (br. s., 1H), 9.12 (br. s., 1H), 8.08 - 8.02 (m, 1H), 7.92 - 7.85 (m, 1H), 7.60 (d, J=6.4 Hz, 1H), 7.35 (t, J=7.9 Hz, 1H), 6.93 - 6.87 (m, 1H), 6.49 (t, J=3.5 Hz, 1H), 5.84 (br. s., 1H), 5.47 (br. s., 1H), 4.69 (td, J=14.8, 2.7 Hz, 2H), 4.63 (d, J=10.1 Hz, 1H), 4.51 (br. s., 1H), 3.97 - 3.90 (m, 1H), 3.70 (dd, J=10.5, 8.4 Hz, 1H), 2.65 (br. s., 1H), 2.40 - 2.25 (m, 2H), 1.89 (br. s., 1H), 1.81 (d, J=6.4 Hz, 1H), 1.73 (br. s., 1H), 1.56 (t, J=19.5 Hz, 4H), 1.49 (br. s., 2H), 1.39 (br. s., 5H), 1.25 (br. s., 3H), 1.24 - 1.21 (m, 4H), 1.18 - 1.13 (m, 1H), 0.93 (d, J=6.7 Hz, 3H), 0.92 - 0.88 (m, 7H), 0.73 (br. s., 1H). MS: MS *m/z* 903.4 (M^++1).

Preparation of Compounds 1111 and 1112



Compound 1111



Compound 1112

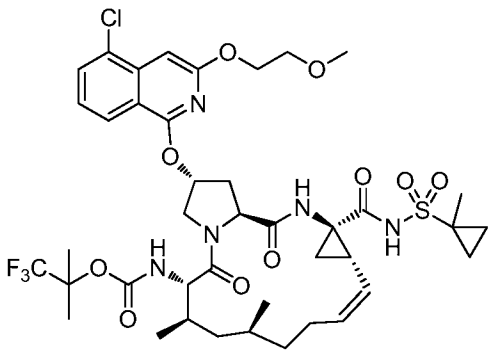
Compounds 1111 and 1112 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1111: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 888.44 (M^++1).

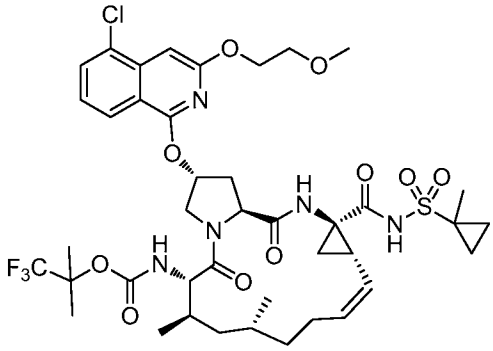
Compound 1112: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2,2-difluoroethoxy)isoquinolin-1-

yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.22 (br. s., 1H), 9.02 (br. s., 1H), 8.03 (d, J=8.2 Hz, 1H), 7.87 (d, J=7.3 Hz, 1H), 7.62 (d, J=7.9 Hz, 1H), 7.35 (t, J=7.9 Hz, 1H), 6.89 (s, 1H), 6.63 - 6.34 (m, 1H), 5.84 (br. s., 1H), 5.51 (br. s., 1H), 5.06 (br. s., 1H), 4.69 (td, J=15.0, 3.4 Hz, 2H), 4.63 (br. s., 1H), 4.49 (d, J=8.5 Hz, 1H), 3.95 - 3.90 (m, 1H), 3.69 (dd, J=10.4, 8.2 Hz, 1H), 2.67 (br. s., 1H), 2.40 - 2.24 (m, 2H), 1.95 - 1.87 (m, 1H), 1.81 (d, J=6.4 Hz, 1H), 1.71 (br. s., 1H), 1.65 - 1.52 (m, J=19.5, 19.5 Hz, 5H), 1.44 (br. s., 1H), 1.35 (d, J=7.3 Hz, 1H), 1.22 (s, 3H), 1.15 (br. s., 2H), 1.09 (br. s., 1H), 1.08 - 1.03 (m, 1H), 1.02 - 0.97 (m, 1H), 0.96 - 0.92 (m, J=6.7 Hz, 4H), 0.92 - 0.88 (m, 7H), 0.75 (d, J=11.0 Hz, 1H). MS: MS *m/z* 888.44 (M^++1).

Preparation of Compounds 1113 and 1114



Compound 1113



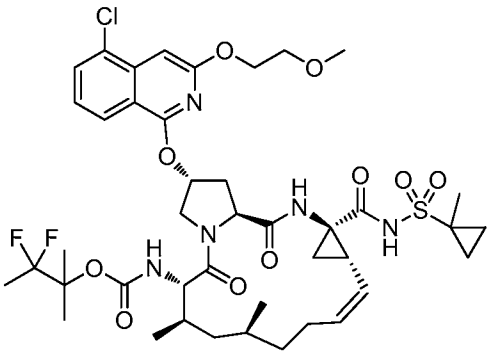
Compound 1114

Compounds 1113 and 1114 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

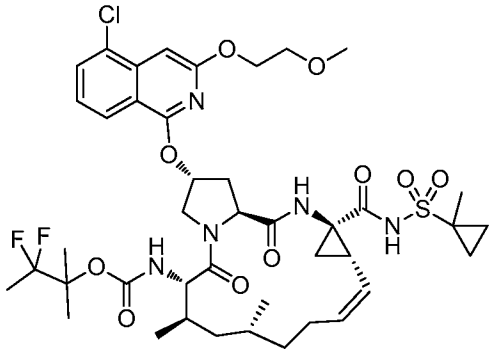
Compound 1113: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 898.6 (M^+-1).

Compound 1114: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.06 (br. s., 1H), 9.16 (br. s., 1H), 8.03 - 7.95 (m, 1H), 7.84 (d, J=7.3 Hz, 2H), 7.32 (t, J=7.9 Hz, 1H), 6.79 (s, 1H), 5.81 (br. s., 1H), 5.52 (br. s., 1H), 4.99 (br. s., 1H), 4.62 (d, J=10.7 Hz, 1H), 4.54 (br. s., 1H), 4.50 - 4.40 (m, 2H), 3.99 - 3.88 (m, 1H), 3.75 (t, J=4.6 Hz, 2H), 3.67 (dd, J=10.5, 8.1 Hz, 1H), 2.65 (br. s., 1H), 2.39 - 2.27 (m, 2H), 1.92 - 1.77 (m, 2H), 1.69 (br. s., 1H), 1.61 (br. s., 1H), 1.50 (br. s., 2H), 1.41 (br. s., 5H), 1.35 (br. s., 2H), 1.30 (s, 4H), 1.25 (br. s., 1H), 1.19 (d, J=18.0 Hz, 2H), 0.98 (s, 3H), 0.93 (d, J=6.7 Hz, 4H), 0.89 (d, J=6.4 Hz, 4H), 0.75 (br. s., 1H). MS: MS *m/z* 898.6 (M^+-1).

Preparation of Compounds 1115 and 1116



Compound 1115



Compound 1116

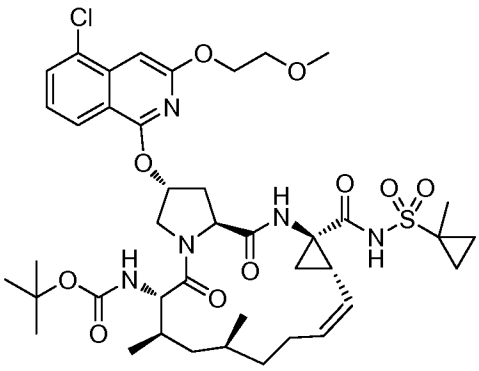
Compounds 1115 and 1116 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1115: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

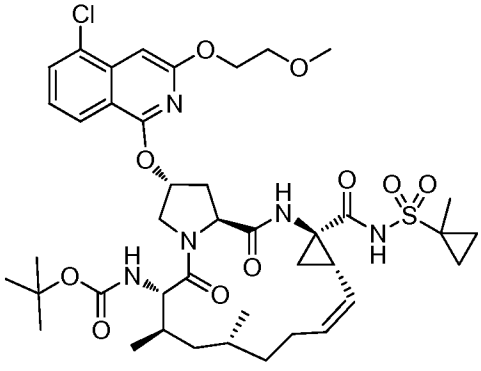
1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 897.5 (M^++1).

Compound 1116: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.06 (br. s., 1H), 9.14 (br. s., 1H), 8.04 - 7.96 (m, 1H), 7.84 (d, J=7.3 Hz, 1H), 7.61 (d, J=7.9 Hz, 1H), 7.31 (t, J=7.9 Hz, 1H), 6.79 (s, 1H), 5.81 (br. s., 1H), 5.53 (br. s., 1H), 4.99 (br. s., 1H), 4.64 (d, J=11.6 Hz, 1H), 4.56 - 4.51 (m, 1H), 4.51 - 4.40 (m, 2H), 3.99 - 3.90 (m, 1H), 3.75 (t, J=4.7 Hz, 2H), 3.68 (dd, J=10.7, 8.2 Hz, 1H), 2.69 (br. s., 2H), 2.42 - 2.27 (m, 2H), 1.94 - 1.86 (m, 1H), 1.82 (d, J=6.1 Hz, 1H), 1.68 (br. s., 1H), 1.56 (t, J=19.7 Hz, 5H), 1.48 - 1.45 (m, 1H), 1.41 (br. s., 4H), 1.35 (d, J=11.3 Hz, 2H), 1.31 - 1.23 (m, 2H), 1.21 (s, 3H), 1.16 (br. s., 2H), 0.93 (d, J=7.0 Hz, 4H), 0.92 - 0.88 (m, 7H), 0.80 - 0.72 (m, 1H). MS: MS *m/z* 897.5 (M^++1).

Preparation of Compounds 1117 and 1118



Compound 1117



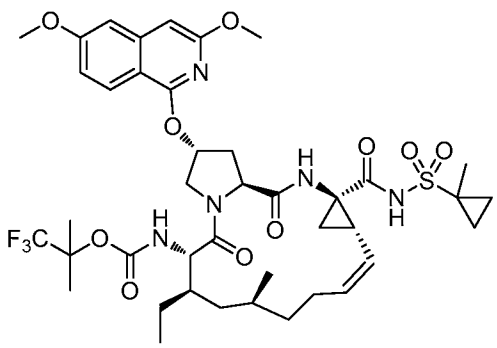
Compound 1118

Compounds 1117 and 1118 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

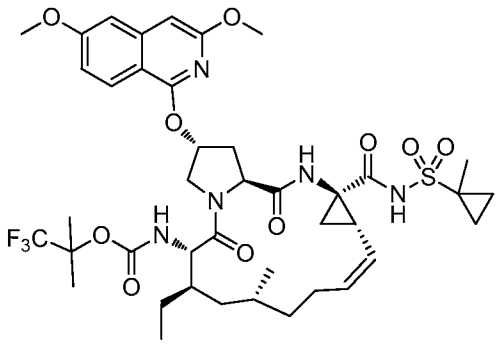
Compound 1117: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 844.49 (M^+-1).

Compound 1118: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-3-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.06 (br. s., 1H), 9.13 (br. s., 1H), 8.03 (d, J=8.5 Hz, 1H), 7.84 - 7.80 (m, 1H), 7.31 - 7.26 (m, 1H), 7.19 (d, J=7.6 Hz, 1H), 6.78 (s, 1H), 5.80 (br. s., 1H), 5.52 (br. s., 1H), 4.98 (br. s., 1H), 4.69 (d, J=11.0 Hz, 1H), 4.55 - 4.47 (m, 1H), 4.47 - 4.39 (m, 2H), 3.95 - 3.90 (m, 1H), 3.75 (t, J=4.7 Hz, 2H), 3.73 - 3.65 (m, 1H), 2.67 (d, J=17.1 Hz, 2H), 2.39 - 2.27 (m, 2H), 1.94 - 1.85 (m, 1H), 1.81 (d, J=6.7 Hz, 1H), 1.71 (s, 1H), 1.62 (br. s., 1H), 1.52 (br. s., 1H), 1.48 - 1.43 (m, 2H), 1.44 - 1.39 (m, 5H), 1.36 (br. s., 2H), 1.32 - 1.22 (m, 1H), 1.22 - 1.10 (m, 1H), 1.06 (s, 9H), 1.04 (br. s., 1H), 0.93 (d, J=7.0 Hz, 3H), 0.88 (d, J=6.4 Hz, 4H), 0.78 - 0.70 (m, 1H). MS: MS *m/z* 844.49 (M^+-1).

Preparation of Compounds 1119 and 1120



Compound 1119



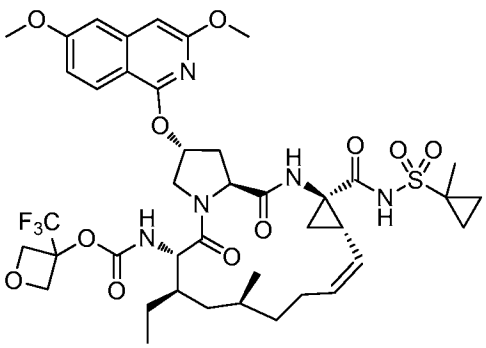
Compound 1120

Compounds 1119 and 1120 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

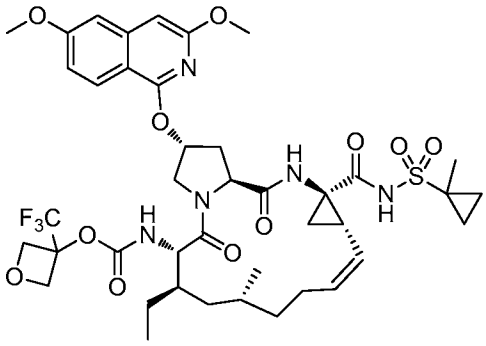
Compound 1119: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 866.43 (M^++1).

Compound 1120: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.03 (br. s., 1H), 9.12 (br. s., 1H), 7.87 (d, J=8.9 Hz, 2H), 7.15 (d, J=2.4 Hz, 1H), 6.90 (dd, J=9.0, 2.3 Hz, 1H), 6.63 (s, 1H), 5.78 (br. s., 1H), 5.52 (br. s., 1H), 4.98 (br. s., 1H), 4.49 (br. s., 2H), 3.95 (dd, J=11.3, 3.7 Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 2.64 (d, J=14.3 Hz, 1H), 2.56 (br. s., 1H), 2.39 - 2.28 (m, 2H), 2.02 - 1.94 (m, 1H), 1.91 - 1.82 (m, 1H), 1.66 - 1.57 (m, 1H), 1.52 (br. s., 3H), 1.42 (s, 5H), 1.39 (br. s., 4H), 1.29 (br. s., 2H), 1.23 (d, J=14.3 Hz, 2H), 1.16 (s, 3H), 1.14 - 1.08 (m, 1H), 1.05 - 0.96 (m, 1H), 0.92 (d, J=6.1 Hz, 3H), 0.90 - 0.82 (m, 1H), 0.75 (t, J=7.5 Hz, 3H). MS: MS *m/z* 866.43 (M^++1).

Preparation of Compounds 1121 and 1122



Compound 1121



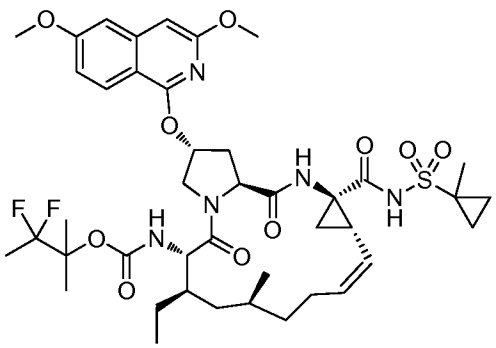
Compound 1122

Compounds 1121 and 1122 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

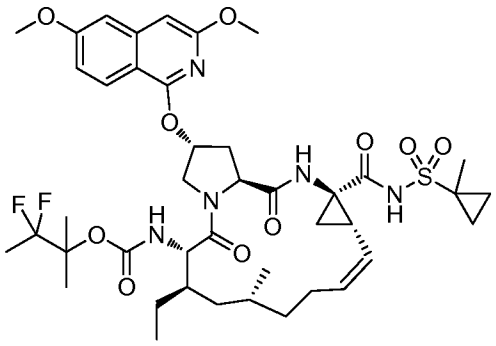
Compound 1121: 3-(trifluoromethyl)oxetan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 880.39 (M^++1).

Compound 1122: 3-(trifluoromethyl)oxetan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.01 (s, 1H), 9.11 (s, 1H), 8.36 (d, J=8.2 Hz, 1H), 7.85 (d, J=9.2 Hz, 1H), 7.16 (d, J=2.1 Hz, 1H), 6.91 (dd, J=9.2, 2.1 Hz, 1H), 6.64 (s, 1H), 5.79 (br. s., 1H), 5.53 (d, J=6.1 Hz, 1H), 5.00 (t, J=10.2 Hz, 1H), 4.70 (d, J=8.5 Hz, 1H), 4.54 (d, J=8.2 Hz, 1H), 4.52 - 4.46 (m, 1H), 4.43 (s, 3H), 4.00 - 3.90 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 2.73 - 2.62 (m, 2H), 2.39 - 2.28 (m, 2H), 2.00 (br. s., 1H), 1.92 (s, 1H), 1.61 (d, J=6.7 Hz, 1H), 1.52 (br. s., 2H), 1.45 (br. s., 4H), 1.41 (s, 3H), 1.36 (br. s., 1H), 1.29 (d, J=9.8 Hz, 1H), 1.17 (br. s., 1H), 1.03 (t, J=11.3 Hz, 1H), 0.93 (d, J=5.5 Hz, 3H), 0.90 (br. s., 2H), 0.75 (t, J=7.5 Hz, 3H). MS: MS *m/z* 880.39 (M^++1).

Preparation of Compounds 1123 and 1124



Compound 1123



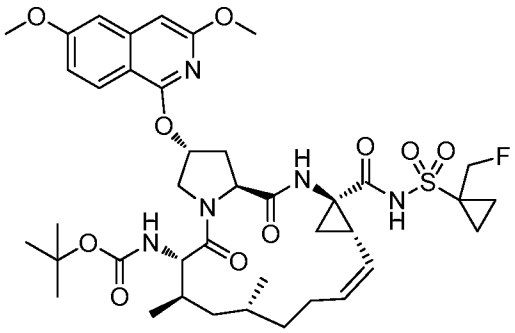
Compound 1124

Compounds 1123 and 1124 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1123: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 862.5 (M^++1).

Compound 1124: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.04 (s, 1H), 9.10 (s, 1H), 7.87 (d, J=8.9 Hz, 1H), 7.69 (d, J=8.5 Hz, 1H), 7.16 (d, J=2.1 Hz, 1H), 6.89 (dd, J=9.0, 2.3 Hz, 1H), 6.63 (s, 1H), 5.79 (br. s., 1H), 5.57 - 5.49 (m, 1H), 4.99 (t, J=9.9 Hz, 1H), 4.57 - 4.44 (m, 2H), 3.99 - 3.92 (m, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 2.76 - 2.59 (m, 2H), 2.40 - 2.27 (m, 2H), 2.00 - 1.87 (m, 2H), 1.65 - 1.57 (m, 3H), 1.56 - 1.49 (m, 3H), 1.46 (br. s., 3H), 1.41 (s, 4H), 1.36 (br. s., 1H), 1.32 (s, 3H), 1.31 - 1.23 (m, 1H), 1.18 (br. s., 1H), 1.08 (s, 3H), 1.02 (t, J=11.7 Hz, 1H), 0.93 (d, J=6.1 Hz, 3H), 0.90 (br. s., 2H), 0.76 (t, J=7.5 Hz, 3H). MS: MS *m/z* 862.5 (M^++1).

Preparation of Compound 1125

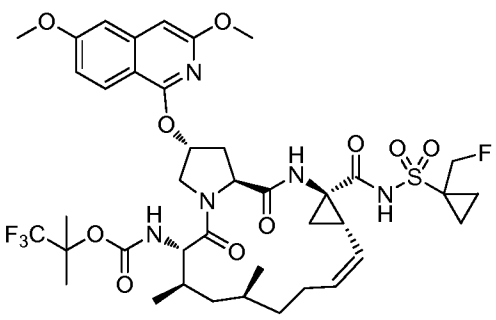


Compound 1125

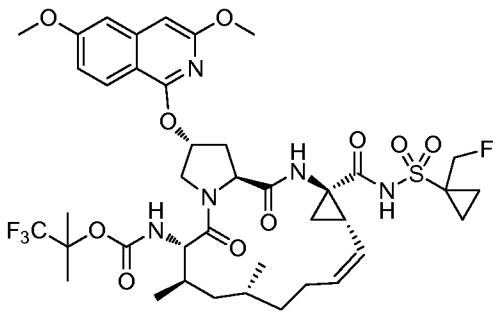
Compound 1125 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1125: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.27 (br. s., 1H), 9.01 (br. s., 1H), 7.92 (d, J=9.2 Hz, 1H), 7.21 (d, J=7.6 Hz, 1H), 7.14 (d, J=2.1 Hz, 1H), 6.86 (dd, J=9.0, 2.3 Hz, 1H), 6.66 - 6.61 (m, 1H), 5.76 (br. s., 1H), 5.51 (br. s., 1H), 5.00 (br. s., 1H), 4.90 - 4.71 (m, J=11.3 Hz, 1H), 4.58 (br. s., 2H), 4.50 (d, J=11.6 Hz, 1H), 4.44 (d, J=9.8 Hz, 1H), 3.95 - 3.91 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.77 - 3.72 (m, 1H), 2.71 - 2.58 (m, 2H), 2.35 - 2.26 (m, 2H), 1.91 (d, J=13.1 Hz, 1H), 1.83 (d, J=6.4 Hz, 1H), 1.70 (br. s., 1H), 1.53 (br. s., 2H), 1.38 (d, J=16.5 Hz, 3H), 1.25 (br. s., 1H), 1.20 (s, 9H), 1.16 (br. s., 1H), 1.08 (br. s., 1H), 0.94 (d, J=7.0 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H), 0.74 (t, J=12.8 Hz, 1H). MS: MS *m/z* 816.5 (M^++1).

Preparation of Compounds 1126 and 1127



Compound 1126



Compound 1127

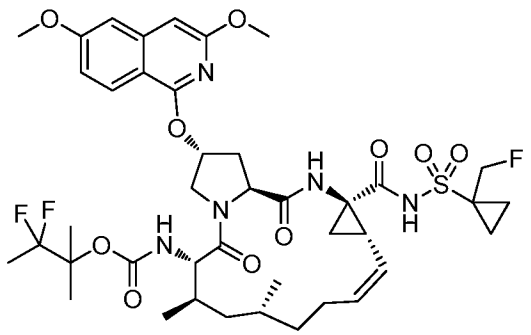
Compounds 1126 and 1127 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1126: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-

(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 870.4 (M^++1).

Compound 1127: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.27 (s, 1H), 9.05 (s, 1H), 7.89 (d, J=9.2 Hz, 1H), 7.85 (d, J=7.6 Hz, 1H), 7.15 (d, J=2.1 Hz, 1H), 6.90 (dd, J=9.2, 2.4 Hz, 1H), 6.62 (s, 1H), 5.77 (br. s., 1H), 5.55 - 5.48 (m, 1H), 5.00 (t, J=9.9 Hz, 1H), 4.62 - 4.44 (m, 3H), 3.95 - 3.91 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.73 (dd, J=10.7, 7.9 Hz, 1H), 2.70 - 2.59 (m, 2H), 2.38 - 2.25 (m, 2H), 1.94 - 1.80 (m, 2H), 1.73 - 1.66 (m, 1H), 1.53 (br. s., 4H), 1.48 - 1.43 (m, 1H), 1.41 (s, 4H), 1.40 - 1.31 (m, 1H), 1.31 - 1.20 (m, 2H), 1.19 (s, 3H), 1.15 (d, J=12.2 Hz, 1H), 0.94 (d, J=7.0 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.76 (t, J=12.1 Hz, 1H). MS: MS *m/z* 870.4 (M^++1).

Preparation of Compound 1128



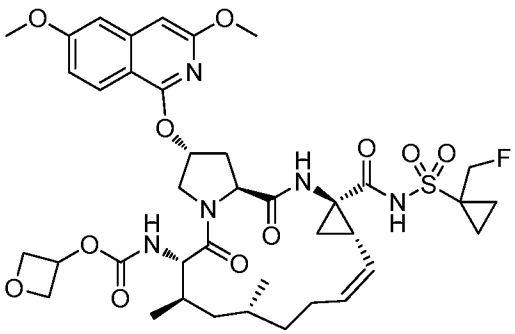
Compound 1128

Compound 1128 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1128: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.27 (s, 1H), 9.02 (s, 1H), 7.89 (d, J=9.2 Hz, 1H), 7.64 (d, J=7.9 Hz, 1H), 7.15 (d, J=2.1 Hz, 1H), 6.89 (dd, J=9.2, 2.4 Hz, 1H), 6.63 (s, 1H), 5.78 (br. s., 1H), 5.55 - 5.48 (m, 1H), 5.01 (t, J=9.6 Hz, 1H), 4.88 - 4.73 (m, J=11.3 Hz, 1H), 4.63 - 4.43 (m, 3H), 3.96 - 3.91 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.77 - 3.71 (m, 1H), 2.72 - 2.60 (m, 2H), 2.39 - 2.27 (m, 2H), 1.96 - 1.87 (m, 1H), 1.87 - 1.79 (m, 1H), 1.73 - 1.65 (m, 1H), 1.65 - 1.55 (m, 4H), 1.55 - 1.50 (m, 3H), 1.49 - 1.33 (m, 2H), 1.32 (s, 3H), 1.31 - 1.20 (m, 2H), 1.15 (d, J=13.7 Hz, 1H), 1.11 (s, 3H), 0.94 (d, J=6.7 Hz, 3H), 0.91 (d, J=6.4 Hz, 3H), 0.76 (t, J=12.1 Hz, 1H). MS: MS *m/z* 866.5 (M^++1).

Preparation of Compound 1129



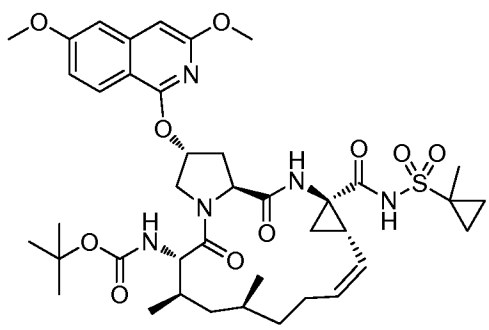
Compound 1129

Compound 1129 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

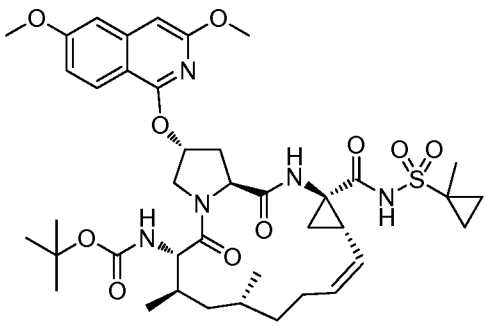
Compound 1129: oxetan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.26 (br. s., 1H), 9.00 (br. s., 1H), 7.89 - 7.80 (m, 2H), 7.17 (d, J=2.1 Hz, 1H), 6.97 (dd, J=8.9, 2.1 Hz, 1H), 6.64 (s, 1H), 5.78 (br. s., 1H), 5.51 (br. s., 1H), 5.02 (br. s., 1H), 4.91 - 4.80 (m, 1H), 4.76 (d, J=9.5 Hz, 1H), 4.64 - 4.52 (m, 2H), 4.48 - 4.40 (m, 3H), 4.34 - 4.29 (m, 1H), 4.14 (dd, J=7.3, 5.5 Hz, 1H), 3.96 - 3.91 (m, 1H), 3.90 (s,

3H), 3.88 (s, 3H), 3.78 - 3.72 (m, 1H), 2.70 - 2.58 (m, 1H), 2.40 - 2.24 (m, 2H), 1.92 (br. s., 1H), 1.85 (br. s., 1H), 1.67 (br. s., 1H), 1.53 (br. s., 3H), 1.44 (br. s., 1H), 1.37 (br. s., 1H), 1.31 - 1.20 (m, 4H), 1.15 (br. s., 1H), 0.93 (d, J=6.7 Hz, 3H), 0.90 (d, J=6.1 Hz, 3H), 0.77 (d, J=11.3 Hz, 1H). MS: MS *m/z* 816.5 (M^++1).

Preparation of Compounds 1130 and 1131



Compound 1130



Compound 1131

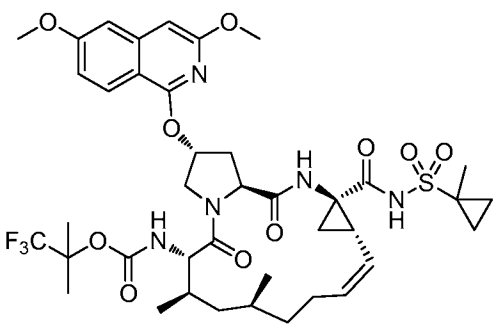
Compounds 1130 and 1131 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1130: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 798.4 (M^++1).

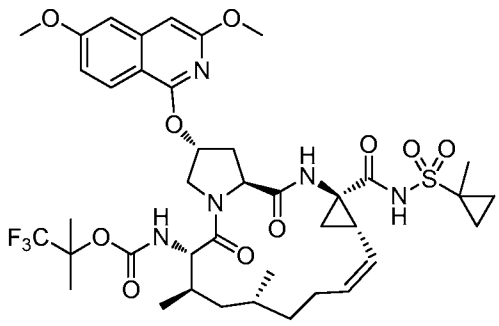
Compound 1131: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.05 (br. s., 1H), 9.09 (br. s., 1H), 7.92 (d, J=8.9 Hz, 1H), 7.21 (d, J=8.2 Hz, 1H), 7.14 (d, J=2.1 Hz, 1H), 6.86 (dd, J=9.0, 2.3 Hz, 1H), 6.61 (s, 1H), 5.77 (br. s., 1H), 5.52 (br. s., 1H), 4.98 (br. s., 1H), 4.58 (d, J=10.7 Hz, 1H), 4.49 - 4.43 (m, 1H), 3.96 -

3.91 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.74 (dd, J=10.4, 8.5 Hz, 1H), 2.76 - 2.67 (m, 1H), 2.67 - 2.58 (m, 1H), 2.39 - 2.26 (m, 2H), 1.95 - 1.87 (m, 1H), 1.87 - 1.78 (m, 1H), 1.74 - 1.65 (m, 1H), 1.61 (br. s., 1H), 1.51 (br. s., 1H), 1.41 (s, 4H), 1.39 - 1.22 (m, 3H), 1.19 (s, 9H), 1.15 (br. s., 2H), 1.07 (br. s., 1H), 0.93 (d, J=7.0 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H), 0.74 (t, J=12.5 Hz, 1H). MS: MS *m/z* 798.4 (M^++1).

Preparation of Compounds 1132 and 1133



Compound 1132



Compound 1133

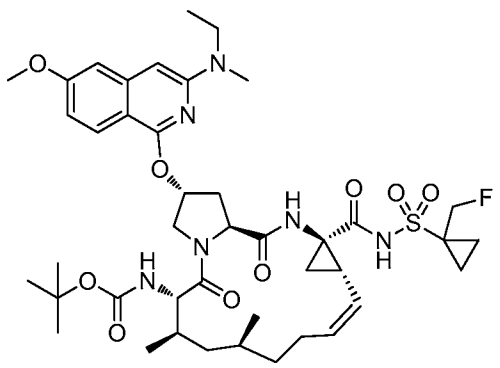
Compounds 1132 and 1133 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1132: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 852.4 (M^++1).

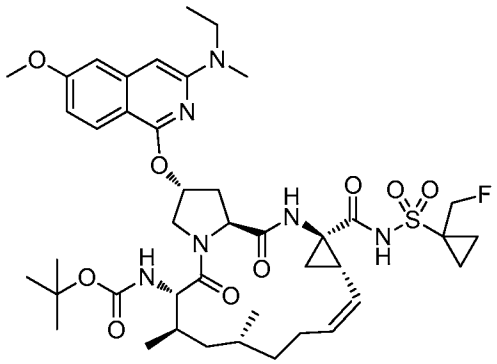
Compound 1133: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.04 (br. s., 1H), 9.13 (br. s., 1H), 7.91 - 7.82 (m, 2H), 7.15 (d, J=2.1 Hz, 1H), 6.90 (dd, J=9.2, 2.4 Hz, 1H), 6.64 - 6.61 (m, 1H), 5.78 (br. s., 1H), 5.53 (br. s., 1H), 4.98 (br. s., 1H), 4.57 - 4.47 (m, 2H), 3.96 - 3.91 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.73

(dd, J=10.7, 7.9 Hz, 1H), 2.73 - 2.60 (m, 2H), 2.39 - 2.28 (m, 2H), 1.94 - 1.81 (m, 2H), 1.69 (br. s., 1H), 1.61 (br. s., 1H), 1.52 (br. s., 1H), 1.49 - 1.43 (m, 2H), 1.40 (s, 6H), 1.36 (br. s., 1H), 1.29 (d, J=8.5 Hz, 3H), 1.16 (s, 3H), 1.14 - 1.06 (m, 1H), 0.93 (d, J=6.7 Hz, 3H), 0.90 (d, J=6.1 Hz, 3H), 0.76 (t, J=12.2 Hz, 1H). MS: MS *m/z* 852.4 (M^++1).

Preparation of Compounds 1134 and 1135



Compound 1134



Compound 1135

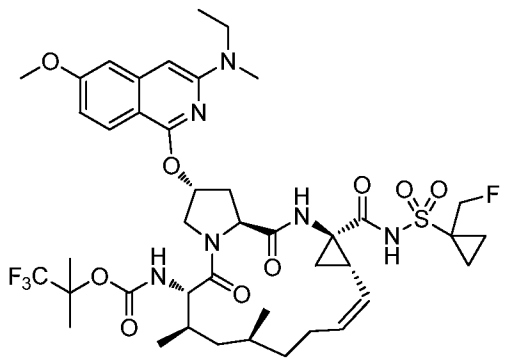
Compounds 1134 and 1135 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1134: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(ethyl(methyl)amino)-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 843.46 (M^++1).

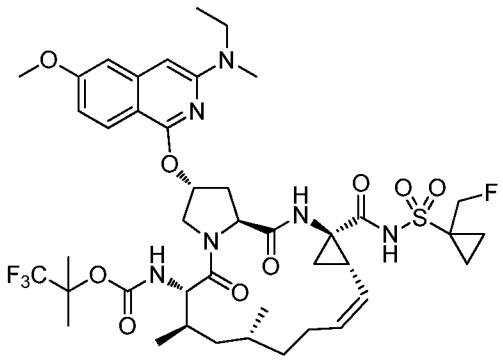
Compound 1135: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(ethyl(methyl)amino)-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, METHANOL-d4) Shift 7.81 (d, J=9.2 Hz, 1H), 6.84 (d, J=2.4 Hz, 1H), 6.60 (dd, J=9.0, 2.3 Hz, 1H), 6.16 (s, 1H), 5.83 (br. s., 1H), 5.57 (d, J=5.8 Hz, 1H), 4.87 - 4.71 (m, 1H), 4.62 (t,

J=10.2 Hz, 2H), 4.57 - 4.51 (m, 2H), 4.09 - 4.05 (m, 1H), 3.96 - 3.90 (m, 1H), 3.86 (s, 3H), 3.73 - 3.65 (m, 2H), 3.06 (s, 3H), 2.75 - 2.68 (m, 1H), 2.63 (br. s., 1H), 2.45 - 2.35 (m, 2H), 1.96 (s, 1H), 1.89 - 1.77 (m, 3H), 1.68 (dd, J=8.2, 5.2 Hz, 2H), 1.62 (br. s., 2H), 1.57 - 1.41 (m, 3H), 1.26 (s, 9H), 1.23 (br. s., 1H), 1.20 (t, J=7.0 Hz, 3H), 1.12 (br. s., 3H), 1.01 (d, J=7.0 Hz, 3H), 0.99 (d, J=6.4 Hz, 3H), 0.82 (t, J=12.7 Hz, 1H). MS: MS *m/z* 843.46 (M^++1).

Preparation of Compounds 1136 and 1137



Compound 1136



Compound 1137

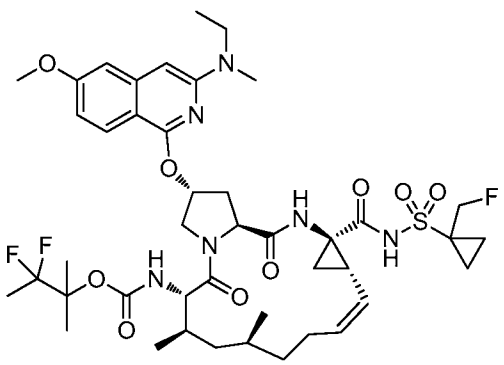
Compounds 1136 and 1137 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1136: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(ethyl(methyl)amino)-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 897.5 (M^++1).

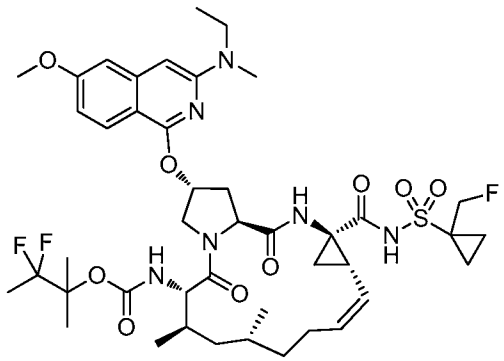
Compound 1137: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(ethyl(methyl)amino)-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, METHANOL-d4) Shift 7.80 (d, J=9.2 Hz, 1H), 6.85 (d, J=2.4 Hz, 1H), 6.61 (dd, J=9.2, 2.4 Hz, 1H), 6.17 (s, 1H), 5.80 (br. s., 1H), 5.55 (td, J=10.1, 5.8 Hz, 1H), 5.21 (br. s., 1H), 4.86 - 4.72 (m, 1H), 4.70 - 4.60 (m, 2H), 4.60 - 4.54 (m, 2H), 4.03 (dd, J=11.3, 3.7 Hz, 1H), 3.88 (s, 1H), 3.86 (s, 3H), 3.77 - 3.64 (m, 2H), 3.06 (s, 3H), 2.72 (dd, J=13.7, 7.3 Hz, 1H), 2.59 (d, J=9.2 Hz, 1H), 2.46 - 2.32 (m, 2H), 2.01 - 1.94 (m, 1H), 1.92 - 1.83 (m, 1H), 1.79 (dd, J=13.3, 4.7 Hz, 1H), 1.68 (dd, J=8.2, 5.2 Hz, 1H), 1.66 - 1.56 (m, 2H), 1.53 (dd, J=9.5, 5.2 Hz, 1H), 1.46 (s, 5H), 1.42 (br. s., 1H), 1.31 - 1.22 (m, 1H), 1.20 (t, J=7.0 Hz, 3H), 1.15 (s, 4H), 1.11 (br. s., 2H), 1.01 (d, J=6.7 Hz, 3H), 0.98 (d, J=6.4 Hz, 3H), 0.84 - 0.76 (m, 1H). MS: MS *m/z* 897.5 (M^++1).

Preparation of Compounds 1138 and 1139



Compound 1138



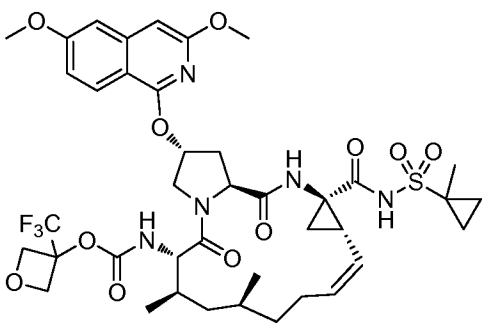
Compound 1139

Compounds 1138 and 1139 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

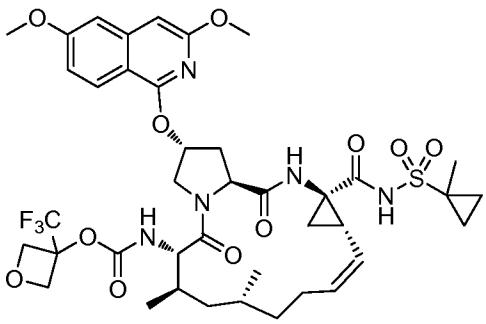
Compound 1138: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(ethyl(methyl)amino)-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 893.41 (M^++1).

Compound 1139: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(ethyl(methyl)amino)-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, METHANOL-d4) Shift 7.80 (d, J=8.9 Hz, 1H), 6.85 (d, J=2.1 Hz, 1H), 6.60 (dd, J=9.2, 2.4 Hz, 1H), 6.17 (s, 1H), 5.82 (br. s., 1H), 5.56 (td, J=10.1, 6.1 Hz, 1H), 5.07 (br. s., 1H), 4.87 - 4.74 (m, 1H), 4.66 - 4.50 (m, 3H), 4.04 (dd, J=11.6, 3.7 Hz, 1H), 3.89 (d, J=10.7 Hz, 1H), 3.86 (s, 3H), 3.74 - 3.64 (m, 2H), 3.05 (s, 3H), 2.75 - 2.60 (m, 2H), 2.44 - 2.32 (m, 2H), 1.98 - 1.83 (m, 2H), 1.77 (dd, J=13.6, 5.6 Hz, 1H), 1.72 - 1.57 (m, 4H), 1.57 - 1.42 (m, 6H), 1.41 - 1.38 (m, 4H), 1.30 (s, 1H), 1.24 (br. s., 1H), 1.20 (t, J=7.0 Hz, 4H), 1.17 - 1.13 (m, 1H), 1.12 (s, 3H), 0.99 (dd, J=9.5, 6.7 Hz, 6H), 0.84 - 0.77 (m, 1H). MS: MS *m/z* 893.41 (M^++1).

Preparation of Compounds 1140 and 1141



Compound 1140



Compound 1141

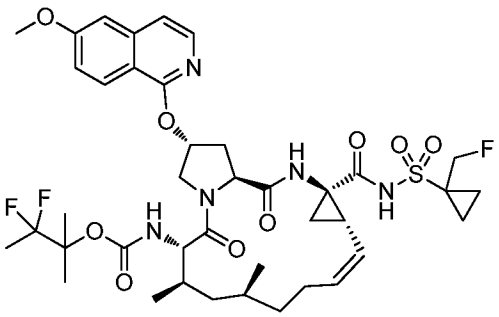
Compounds 1140 and 1141 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1140: 3-(trifluoromethyl)oxetan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

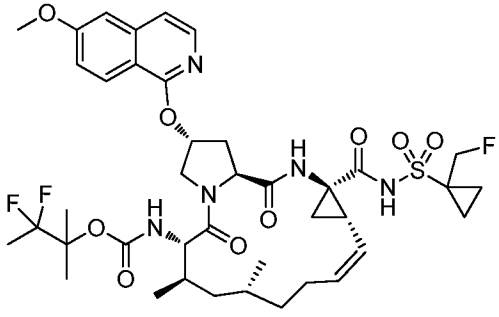
1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 866.4 (M^++1).

Compound 1141: 3-(trifluoromethyl)oxetan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.01 (br. s., 1H), 9.10 (br. s., 1H), 8.29 (d, J=7.9 Hz, 1H), 7.85 (d, J=9.2 Hz, 1H), 7.16 (d, J=2.4 Hz, 1H), 6.90 (dd, J=9.0, 2.3 Hz, 1H), 6.63 (s, 1H), 5.78 (br. s., 1H), 5.52 (br. s., 1H), 5.00 (br. s., 1H), 4.72 (d, J=8.9 Hz, 1H), 4.53 - 4.36 (m, 5H), 3.96 (dd, J=11.4, 3.2 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.80 - 3.74 (m, 1H), 2.64 (d, J=11.6 Hz, 1H), 2.39 - 2.26 (m, 2H), 1.93 - 1.84 (m, 2H), 1.71 (br. s., 1H), 1.59 (br. s., 1H), 1.51 (br. s., 1H), 1.47 - 1.42 (m, 2H), 1.40 (br. s., 3H), 1.37 - 1.31 (m, 2H), 1.26 (d, J=7.3 Hz, 1H), 1.17 (br. s., 1H), 0.93 (d, J=7.0 Hz, 4H), 0.91 (d, J=6.4 Hz, 3H), 0.88 - 0.82 (m, 1H), 0.77 (br. s., 1H). MS: MS *m/z* 866.4 (M^++1).

Preparation of Compounds 1142 and 1143



Compound 1142



Compound 1143

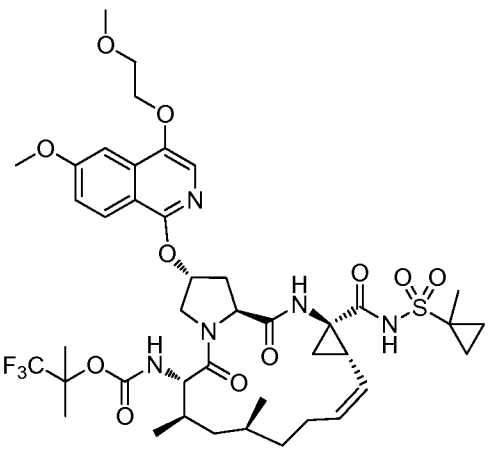
Compounds 1142 and 1143 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1142: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-

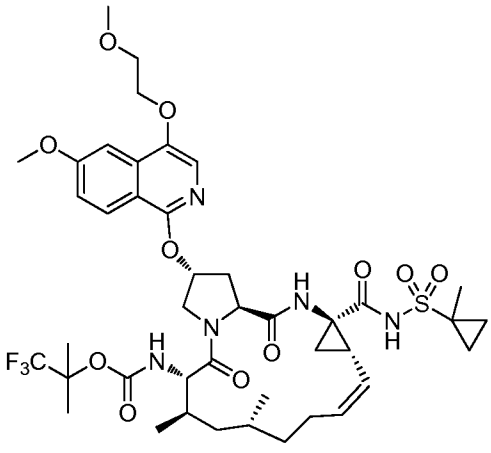
(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 836.44 (M^++1).

Compound 1143: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.28 (s, 1H), 9.03 (s, 1H), 8.02 (d, J=9.2 Hz, 1H), 7.97 (d, J=6.1 Hz, 1H), 7.63 (d, J=8.2 Hz, 1H), 7.35 - 7.30 (m, 2H), 7.14 (dd, J=9.2, 2.4 Hz, 1H), 5.82 (br. s., 1H), 5.55 - 5.48 (m, 1H), 5.00 (t, J=10.1 Hz, 1H), 4.88 - 4.72 (m, 1H), 4.63 - 4.42 (m, 3H), 3.96 - 3.91 (m, 2H), 3.90 (s, 3H), 3.73 (dd, J=10.5, 8.4 Hz, 1H), 2.72 - 2.59 (m, 2H), 2.36 - 2.27 (m, 2H), 1.95 - 1.86 (m, 1H), 1.86 - 1.78 (m, 1H), 1.70 (dd, J=13.1, 6.1 Hz, 1H), 1.64 - 1.55 (m, 4H), 1.53 (br. s., 2H), 1.44 (br. s., 1H), 1.41 - 1.32 (m, 1H), 1.30 (s, 3H), 1.29 - 1.20 (m, 2H), 1.15 (d, J=13.1 Hz, 1H), 1.07 (s, 3H), 0.94 (d, J=6.7 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.76 (t, J=12.8 Hz, 1H). MS: MS *m/z* 836.44 (M^++1).

Preparation of Compounds 1144 and 1145



Compound 1144



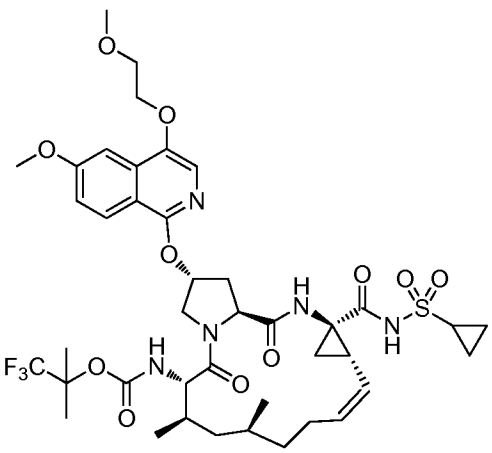
Compound 1145

Compounds 1144 and 1145 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

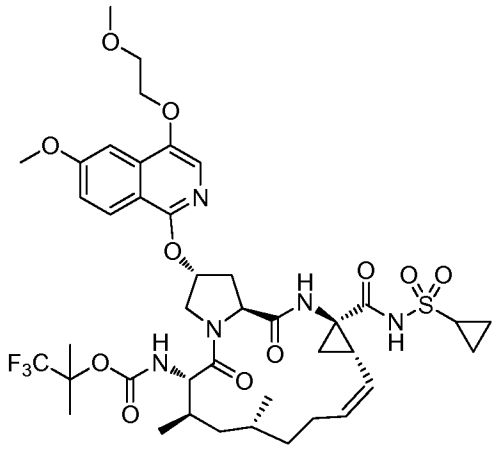
Compound 1144: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 896.8 (M^++1).

Compound 1145: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.06 (br. s., 1H), 9.11 (br. s., 1H), 8.00 (d, J=9.2 Hz, 1H), 7.81 (d, J=7.6 Hz, 1H), 7.66 (s, 1H), 7.37 (d, J=2.4 Hz, 1H), 7.20 (dd, J=9.0, 2.6 Hz, 1H), 5.75 (br. s., 1H), 5.49 (br. s., 1H), 5.03 (br. s., 1H), 4.48 (br. s., 2H), 4.30 - 4.24 (m, 2H), 3.92 (s, 3H), 3.89 (d, J=3.7 Hz, 1H), 3.81 - 3.76 (m, 2H), 3.71 (dd, J=10.5, 8.1 Hz, 1H), 3.39 (s, 3H), 2.56 (br. s., 1H), 2.35 - 2.25 (m, 2H), 1.91 - 1.78 (m, 2H), 1.73 (br. s., 1H), 1.57 (br. s., 1H), 1.51 (br. s., 1H), 1.39 (br. s., 4H), 1.38 (s, 5H), 1.35 - 1.30 (m, 1H), 1.25 (br. s., 1H), 1.19 (d, J=14.3 Hz, 2H), 1.12 (s, 3H), 0.93 (d, J=7.0 Hz, 3H), 0.88 (d, J=6.4 Hz, 3H), 0.86 - 0.80 (m, 1H), 0.74 (d, J=11.3 Hz, 1H). MS: MS *m/z* 896.8 (M^++1).

Preparation of Compounds 1146 and 1147



Compound 1146



Compound 1147

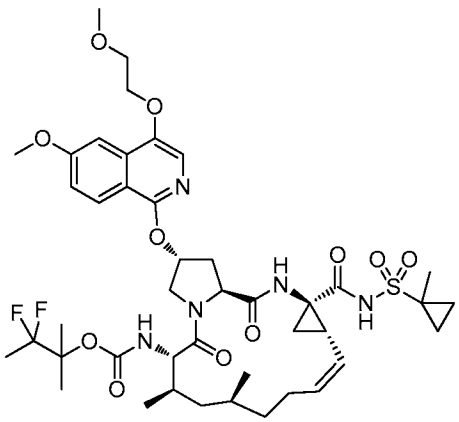
Compounds 1146 and 1147 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1146: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 882.8 (M^++1).

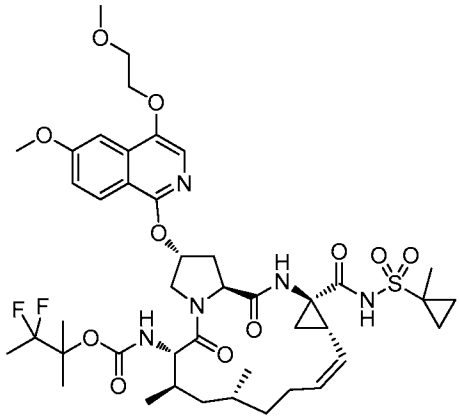
Compound 1147: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.19 (br. s., 1H), 9.13 - 8.85 (m, 1H), 8.00 (d, J=9.2 Hz, 1H), 7.82 (d, J=7.9 Hz, 1H), 7.67 - 7.64 (m, 1H), 7.37 (d, J=2.4 Hz, 1H), 7.20 (dd, J=9.2, 2.4 Hz, 1H), 5.74 (br. s., 1H), 5.52 (br. s., 1H), 4.53 - 4.43 (m, 2H), 4.30 - 4.22 (m, 2H), 3.92 (s, 3H), 3.88 (dd, J=11.4, 3.5 Hz, 1H), 3.82 - 3.77 (m, 2H), 3.71 (dd, J=10.8, 8.1 Hz, 2H), 3.39 (s, 3H), 2.65 (br. s., 1H), 2.60 (br. s., 1H), 2.33 - 2.25 (m, 2H), 1.92 - 1.78 (m, 2H), 1.71 (br. s., 1H), 1.62 - 1.58 (m, 2H), 1.56 (br. s., 1H), 1.51 (br. s., 1H), 1.41 (br. s., 1H), 1.38

(s, 4H), 1.14 (s, 4H), 0.98 (br. s., 3H), 0.94 (d, J=7.0 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H), 0.73 (t, J=12.4 Hz, 1H). MS: MS *m/z* 882.8 (M^++1).

Preparation of Compounds 1148 and 1149



Compound 1148



Compound 1149

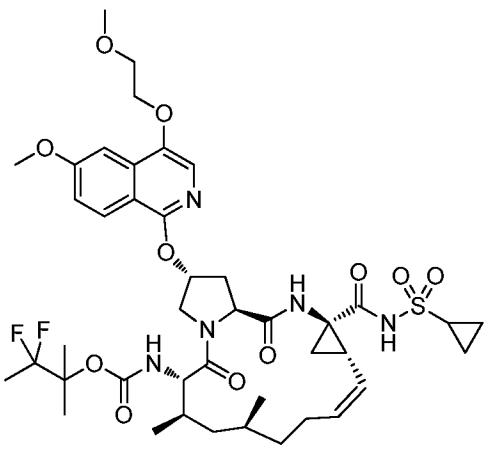
Compounds 1148 and 1149 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1148: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 892.8 (M^++1).

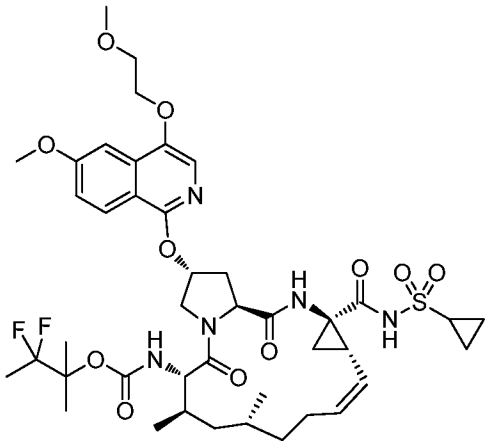
Compound 1149: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 8.01 (d, J=8.9 Hz, 1H), 7.66 (s, 1H), 7.56 (d, J=7.9 Hz, 1H), 7.36 (d, J=2.4 Hz, 1H), 7.19 (dd, J=9.2, 2.4 Hz, 1H), 5.73 (br. s., 1H), 5.51 - 5.25 (m, 1H), 4.42 (br. s., 2H), 4.27 (d, J=3.1 Hz, 2H), 3.91 (s, 3H), 3.89 (br. s., 1H), 3.79 (t, J=4.4 Hz, 2H), 3.73 (t,

J=9.6 Hz, 1H), 3.39 (s, 3H), 2.30 (t, J=9.8 Hz, 2H), 1.86 (d, J=13.1 Hz, 1H), 1.79 (br. s., 2H), 1.57 (t, J=19.7 Hz, 3H), 1.43 (br. s., 2H), 1.34 (br. s., 6H), 1.30 (s, 4H), 1.25 (br. s., 3H), 1.16 (br. s., 2H), 1.05 (s, 3H), 0.92 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.4 Hz, 4H), 0.68 (br. s., 1H). MS: MS *m/z* 892.8 (M^++1).

Preparation of Compounds 1150 and 1151



Compound 1150



Compound 1151

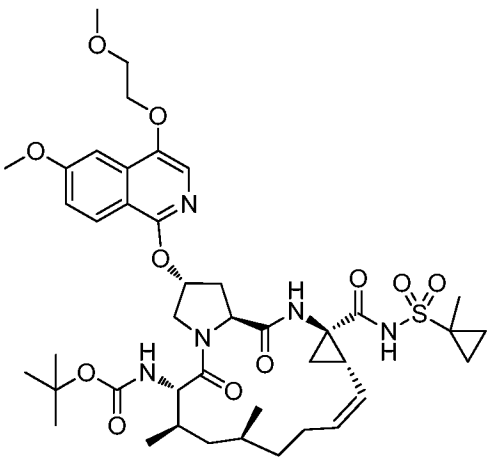
Compounds 1150 and 1151 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1150: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 878.56 (M^++1).

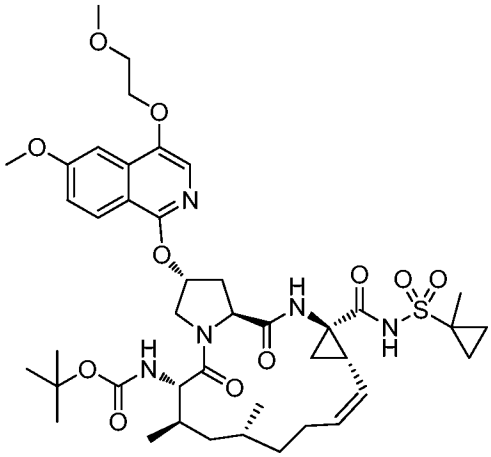
Compound 1151: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.65 - 10.88 (m, 1H), 9.17 - 8.67 (m, 1H), 8.00 (d, J=9.2 Hz, 1H), 7.66 (s, 1H), 7.57

(d, J=6.4 Hz, 1H), 7.36 (d, J=2.4 Hz, 1H), 7.19 (dd, J=9.0, 2.3 Hz, 1H), 5.73 (br. s., 1H), 5.39 (br. s., 1H), 4.41 (br. s., 2H), 4.27 (d, J=2.7 Hz, 2H), 3.91 (s, 3H), 3.88 (br. s., 2H), 3.81 - 3.77 (m, 2H), 3.73 (t, J=9.6 Hz, 1H), 3.39 (s, 3H), 2.33 - 2.24 (m, 2H), 1.89 (br. s., 1H), 1.80 (br. s., 2H), 1.73 - 1.63 (m, 1H), 1.58 (t, J=19.5 Hz, 4H), 1.48 (br. s., 1H), 1.43 (br. s., 1H), 1.38 (br. s., 2H), 1.30 (s, 3H), 1.25 (br. s., 2H), 1.16 (br. s., 1H), 1.06 (s, 3H), 1.01 - 0.96 (m, 1H), 0.93 (d, J=6.7 Hz, 3H), 0.89 (d, J=6.1 Hz, 3H), 0.85 - 0.74 (m, 2H), 0.69 (br. s., 1H). MS: MS *m/z* 878.56 (M^++1).

Preparation of Compounds 1152 and 1153



Compound 1152



Compound 1153

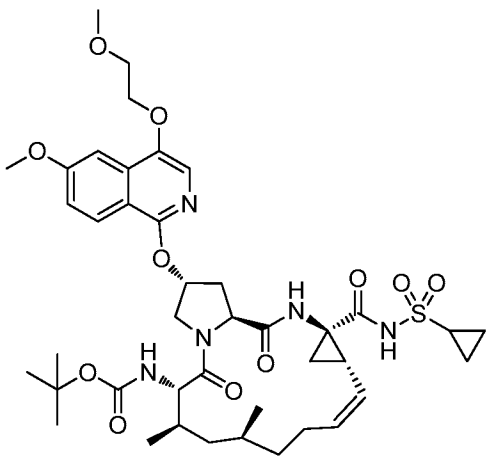
Compounds 1152 and 1153 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1152: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 842.6 (M^++1).

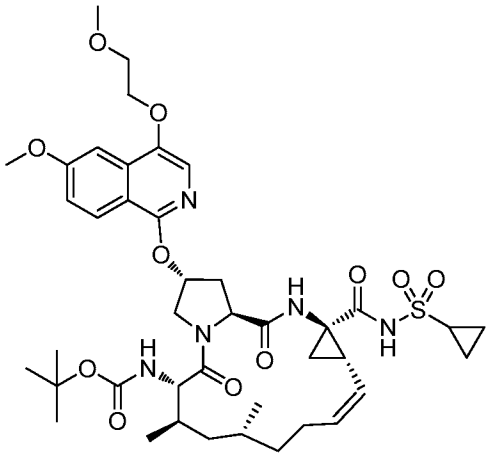
Compound 1153: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.04 (br. s., 1H), 9.06 (s, 1H), 8.03 (d, J=9.2 Hz, 1H), 7.65 (s, 1H), 7.36 (d, J=2.1 Hz, 1H), 7.19 - 7.12 (m, 2H), 5.74 (br. s., 1H), 5.48 (br. s., 1H), 4.50 (br. s., 1H), 4.43 (br. s., 1H), 4.27 (br. s., 2H), 3.92 (s, 3H), 3.89 (br. s., 2H), 3.80 - 3.77 (m, 2H), 3.76 - 3.68 (m, 1H), 3.39 (s, 3H), 2.29 (d, J=9.8 Hz, 2H), 1.88 (br. s., 1H), 1.81 (br. s., 1H), 1.74 (br. s., 1H), 1.61 - 1.44 (m, 2H), 1.38 (br. s., 5H), 1.26 (d, J=14.6 Hz, 4H), 1.16 (s, 9H), 1.06 (br. s., 3H), 0.93 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.4 Hz, 4H), 0.70 (br. s., 1H). MS: MS *m/z* 842.6 (M^++1).

Preparation of Compounds 1154 and 1155



Compound 1154



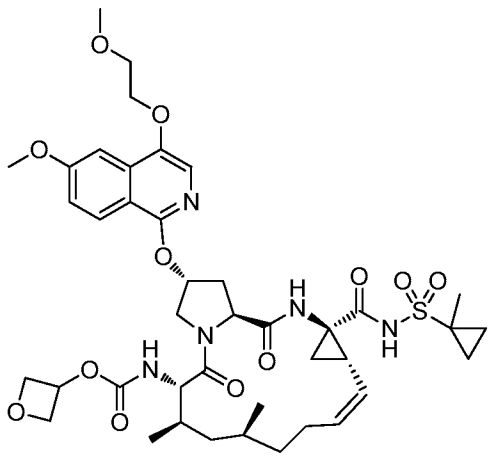
Compound 1155

Compounds 1154 and 1155 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

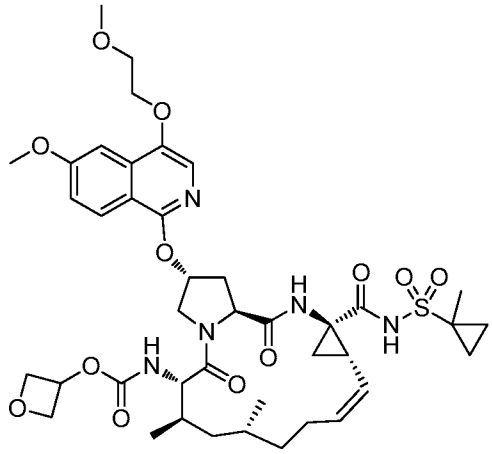
Compound 1154: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 828.6 (M^++1).

Compound 1155: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.22 (s, 1H), 8.88 (d, J=18.6 Hz, 1H), 8.03 (d, J=9.2 Hz, 1H), 7.65 (s, 1H), 7.36 (d, J=2.1 Hz, 1H), 7.19 - 7.13 (m, 2H), 5.73 (br. s., 1H), 5.48 (br. s., 1H), 4.51 (br. s., 1H), 4.40 (br. s., 1H), 4.26 (d, J=4.9 Hz, 2H), 3.92 (s, 4H), 3.88 (d, J=7.6 Hz, 1H), 3.81 - 3.76 (m, 2H), 3.76 - 3.70 (m, 1H), 3.39 (s, 3H), 2.84 (br. s., 1H), 2.32 - 2.24 (m, 2H), 1.94 - 1.85 (m, 1H), 1.80 (br. s., 1H), 1.73 (br. s., 1H), 1.56 (br. s., 1H), 1.40 (br. s., 1H), 1.35 (br. s., 2H), 1.25 (br. s., 1H), 1.21 - 1.14 (m, 10H), 1.07 (br. s., 3H), 0.95 - 0.92 (m, J=6.7 Hz, 4H), 0.90 - 0.86 (m, J=6.1 Hz, 4H), 0.70 (br. s., 1H). MS: MS *m/z* 828.6 (M^++1).

Preparation of Compounds 1156 and 1157



Compound 1156



Compound 1157

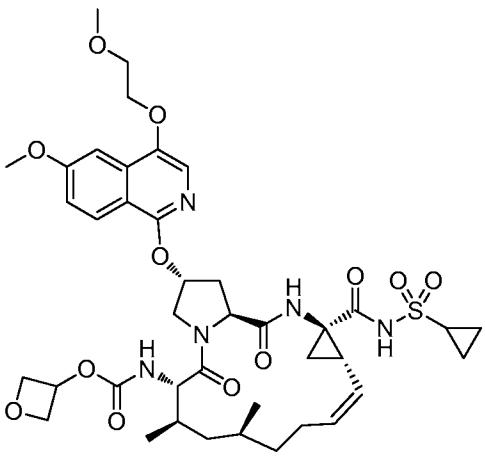
Compounds 1156 and 1157 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1156: oxetan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

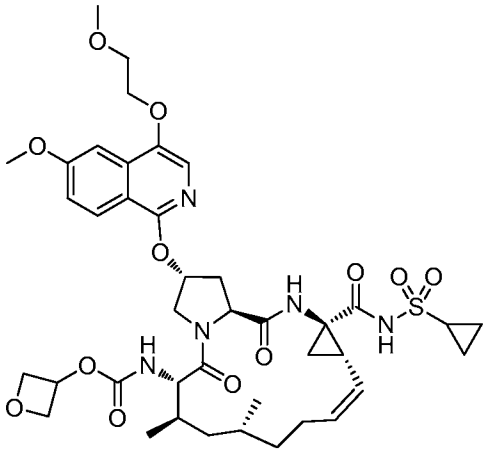
1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 842.5 (M^++1).

Compound 1157: oxetan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.04 (br. s., 1H), 9.10 (br. s., 1H), 7.98 (d, J=9.2 Hz, 1H), 7.82 (d, J=8.9 Hz, 1H), 7.64 (s, 1H), 7.39 (d, J=2.4 Hz, 1H), 7.28 (dd, J=9.2, 2.4 Hz, 1H), 5.76 (br. s., 1H), 5.52 (br. s., 1H), 4.99 (br. s., 1H), 4.81 - 4.78 (m, 1H), 4.54 - 4.45 (m, 2H), 4.38 (t, J=6.9 Hz, 2H), 4.31 - 4.26 (m, 3H), 4.10 (t, J=6.4 Hz, 1H), 3.93 (s, 3H), 3.93 - 3.88 (m, 2H), 3.81 - 3.78 (m, 2H), 3.76 - 3.69 (m, J=8.9 Hz, 1H), 3.40 (s, 3H), 2.75 - 2.66 (m, 1H), 2.59 (br. s., 1H), 2.29 (br. s., 2H), 1.92 (s, 1H), 1.84 (br. s., 1H), 1.67 (br. s., 1H), 1.60 (br. s., 1H), 1.55 - 1.47 (m, 1H), 1.40 (br. s., 4H), 1.37 - 1.32 (m, 1H), 1.26 (d, J=10.4 Hz, 2H), 1.14 (br. s., 1H), 0.93 (d, J=7.0 Hz, 3H), 0.89 (d, J=6.1 Hz, 4H), 0.74 (br. s., 1H). MS: MS *m/z* 842.5 (M^++1).

Preparation of Compounds 1158 and 1159



Compound 1158



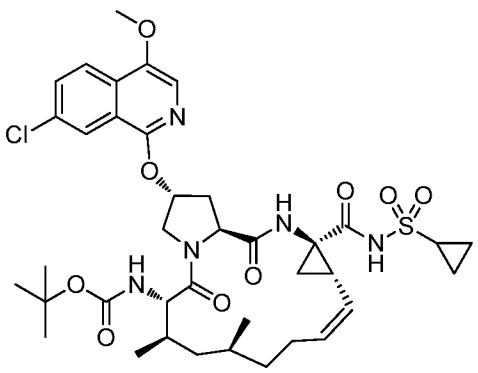
Compound 1159

Compounds 1158 and 1159 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

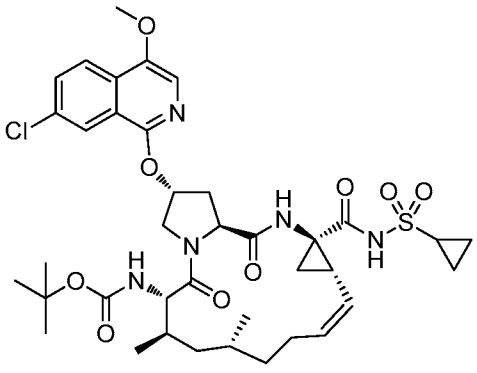
Compound 1158: oxetan-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 828.5 (M^++1).

Compound 1159: oxetan-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxy-4-(2-methoxyethoxy)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.18 (br. s., 1H), 8.97 (br. s., 1H), 7.98 (d, J=9.2 Hz, 1H), 7.82 (d, J=8.2 Hz, 1H), 7.64 (s, 1H), 7.38 (d, J=2.4 Hz, 1H), 7.28 (dd, J=9.0, 2.6 Hz, 1H), 5.75 (br. s., 1H), 5.52 (br. s., 1H), 5.06 (br. s., 1H), 4.82 (quin, J=5.8 Hz, 1H), 4.53 (t, J=6.7 Hz, 1H), 4.47 - 4.37 (m, 3H), 4.32 - 4.26 (m, 4H), 4.13 - 4.10 (m, 1H), 3.93 (s, 3H), 3.92 - 3.87 (m, 1H), 3.81 - 3.78 (m, 2H), 3.75 - 3.71 (m, 1H), 3.40 (s, 3H), 2.69 (br. s., 1H), 2.59 (br. s., 1H), 2.29 (t, J=9.6 Hz, 2H), 1.92 (s, 1H), 1.84 (br. s., 1H), 1.69 (br. s., 1H), 1.60 (br. s., 1H), 1.55 (br. s., 1H), 1.44 (br. s., 1H), 1.37 (br. s., 1H), 1.12 (br. s., 3H), 1.04 - 0.97 (m, 2H), 0.93 (d, J=6.7 Hz, 3H), 0.89 (d, J=6.1 Hz, 3H), 0.74 (br. s., 1H). MS: MS *m/z* 828.5 (M^++1).

Preparation of Compounds 1160 and 1161



Compound 1160



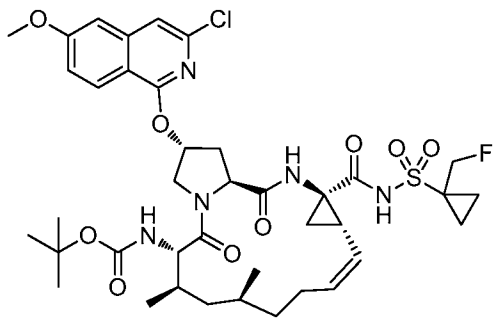
Compound 1161

Compounds 1160 and 1161 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

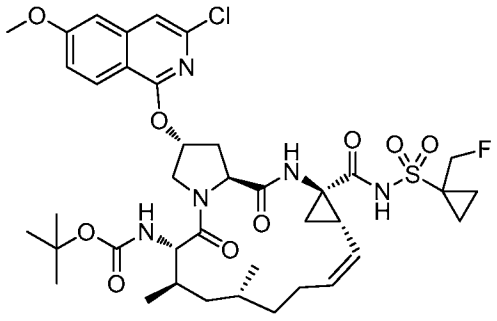
Compound 1160: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-chloro-4-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 788.4 (M^++1).

Compound 1161: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-chloro-4-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500 MHz, CHLOROFORM-d) d ppm 0.74 - 0.84 (m, 2 H) 0.86 (d, J=6.41 Hz, 1 H) 0.88 - 0.94 (m, 1 H) 0.97 (t, J=5.95 Hz, 6 H) 1.06 - 1.16 (m, 9 H) 1.40 - 1.54 (m, 4 H) 1.64 - 1.71 (m, 1 H) 1.74 - 1.87 (m, 1 H) 1.88 - 1.99 (m, 2 H) 2.22 - 2.35 (m, 1 H) 2.43 - 2.54 (m, 1 H) 2.63 - 2.71 (m, 1 H) 2.75 (q, J=8.65 Hz, 1 H) 2.83 - 2.96 (m, 1 H) 3.89 (t, J=9.92 Hz, 1 H) 3.97 - 4.00 (m, 3 H) 4.01 (d, J=3.66 Hz, 1 H) 4.43 - 4.59 (m, 1 H) 4.67 (d, J=10.99 Hz, 1 H) 4.92 (t, J=9.31 Hz, 1 H) 5.49 - 5.59 (m, 1 H) 5.72 - 5.89 (m, 2 H) 7.40 - 7.52 (m, 1 H) 7.56 - 7.65 (m, 1 H) 7.98 (d, J=1.83 Hz, 1 H) 8.00 - 8.11 (m, 1 H) 10.42 - 10.57 (m, 1 H). MS: MS *m/z* 788.4 (M^++1).

Preparation of Compound 1162 and 1163



Compound 1162



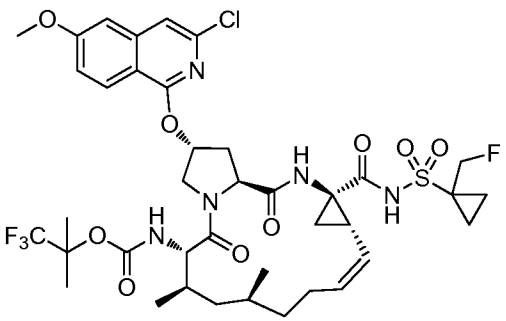
Compound 1163

Compounds 1162 and 1163 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

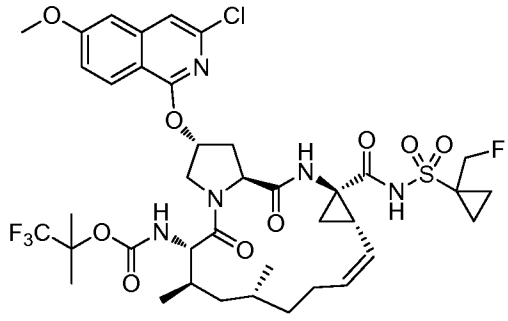
Compound 1162: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-chloro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 820.4 (M^++1).

Compound 1163: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-chloro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.26 (s, 1H), 8.99 (br. s., 1H), 8.03 (d, J=8.9 Hz, 1H), 7.46 (s, 1H), 7.32 (d, J=2.1 Hz, 1H), 7.20 (d, J=7.6 Hz, 1H), 7.12 (dd, J=9.2, 2.4 Hz, 1H), 5.75 (br. s., 1H), 5.51 (d, J=6.7 Hz, 1H), 5.02 (t, J=9.5 Hz, 1H), 4.76 (d, J=11.9 Hz, 1H), 4.65 - 4.55 (m, 1H), 4.55 - 4.36 (m, 2H), 3.94 - 3.87 (m, 4H), 3.70 (dd, J=10.4, 8.2 Hz, 1H), 2.71 - 2.59 (m, 2H), 2.39 - 2.25 (m, 2H), 1.91 (d, J=17.1 Hz, 1H), 1.80 (br. s., 1H), 1.69 (br. s., 1H), 1.53 (br. s., 3H), 1.47 - 1.31 (m, 2H), 1.31 - 1.19 (m, 3H), 1.15 (s, 9H), 1.08 (d, J=7.0 Hz, 1H), 0.94 (d, J=7.0 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H), 0.74 (t, J=12.1 Hz, 1H). MS: MS *m/z* 820.4 (M^++1).

Preparation of Compound 1164 and 1165



Compound 1164



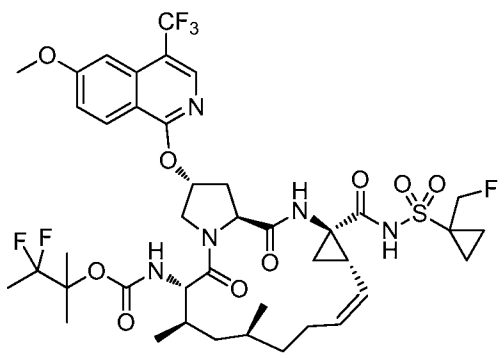
Compound 1165

Compounds 1164 and 1165 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

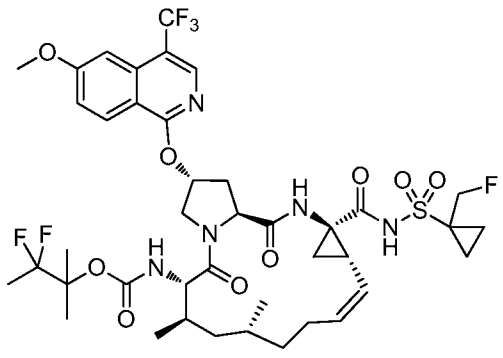
Compound 1164: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-chloro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 874.4 (M^++1).

Compound 1165: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-chloro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.26 (br. s., 1H), 9.03 (br. s., 1H), 8.19 (br. s., 1H), 8.00 (d, J=9.2 Hz, 1H), 7.47 (br. s., 1H), 7.33 (s, 1H), 7.17 (dd, J=9.2, 2.4 Hz, 1H), 5.75 (br. s., 1H), 5.52 (br. s., 1H), 5.03 (br. s., 1H), 4.68 (br. s., 1H), 4.57 (br. s., 1H), 4.47 (br. s., 2H), 3.93 - 3.87 (m, 4H), 3.69 (br. s., 1H), 3.19 - 3.13 (m, 1H), 2.65 (br. s., 1H), 2.32 (d, J=11.0 Hz, 2H), 1.84 (br. s., 2H), 1.71 (br. s., 1H), 1.54 (br. s., 2H), 1.37 (s, 3H), 1.27 (br. s., 6H), 1.18 (dd, J=14.8, 7.5 Hz, 2H), 1.11 (br. s., 3H), 0.93 (d, J=6.1 Hz, 3H), 0.89 (br. s., 3H), 0.74 (br. s., 1H). MS: MS *m/z* 874.4 (M^++1).

Preparation of Compounds 1166 and 1167



Compound 1166



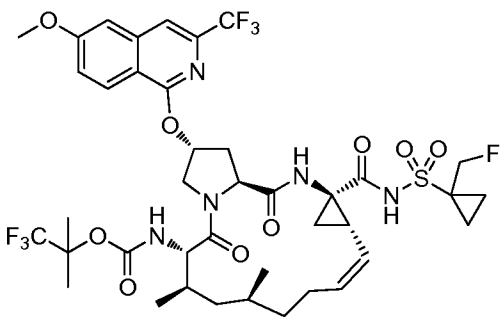
Compound 1167

Compounds 1166 and 1167 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

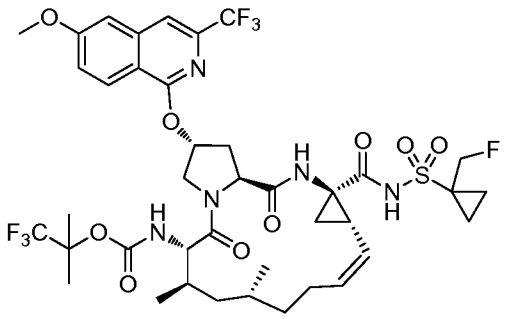
Compound 1166: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxy-4-(trifluoromethyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 904.5 (M^++1).

Compound 1167: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxy-4-(trifluoromethyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.30 (s, 1H), 9.09 (s, 1H), 8.47 (s, 1H), 8.18 (d, J=9.2 Hz, 1H), 7.59 (d, J=8.2 Hz, 1H), 7.37 (dd, J=9.2, 2.1 Hz, 1H), 7.22 (s, 1H), 5.86 (br. s., 1H), 5.55 - 5.49 (m, 1H), 4.99 (t, J=10.1 Hz, 1H), 4.89 - 4.73 (m, 1H), 4.67 (d, J=13.1 Hz, 1H), 4.62 - 4.51 (m, 2H), 3.95 (s, 3H), 3.91 (br. s., 1H), 3.66 - 3.62 (m, 1H), 2.67 (d, J=9.5 Hz, 2H), 2.41 - 2.27 (m, 3H), 1.93 - 1.86 (m, 1H), 1.79 (br. s., 1H), 1.66 (br. s., 1H), 1.59 - 1.48 (m, 7H), 1.43 (br. s., 1H), 1.36 (d, J=14.3 Hz, 1H), 1.25 (d, J=13.4 Hz, 2H), 1.15 (s, 3H), 0.94 (d, J=7.0 Hz, 3H), 0.88 (d, J=6.1 Hz, 3H), 0.77 (s, 3H), 0.76 - 0.70 (m, 1H). MS: MS *m/z* 904.5 (M^++1).

Preparation of Compounds 1168 and 1169



Compound 1168



Compound 1169

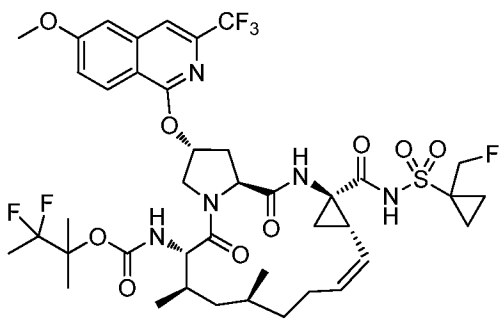
Compounds 1168 and 1169 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1168: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxy-3-(trifluoromethyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 908.45 (M^++1).

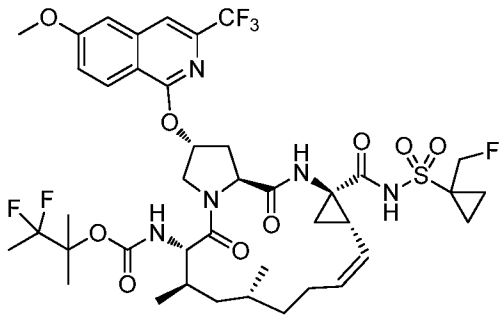
Compound 1169: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxy-3-(trifluoromethyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.26 (s, 1H), 9.02 (s, 1H), 8.11 (d, J=9.2 Hz, 1H), 7.93 (s, 1H), 7.85 (d, J=7.9 Hz, 1H), 7.60 (d, J=2.1 Hz, 1H), 7.35 (dd, J=9.0, 2.3 Hz, 1H), 5.82 (br. s., 1H), 5.55 - 5.49 (m, 1H), 5.02 (t, J=10.1 Hz, 1H), 4.90 - 4.70 (m, 1H), 4.59 (t, J=11.9 Hz, 2H), 4.54 - 4.48 (m, 1H), 3.96 - 3.91 (m, 4H), 3.69 (dd, J=10.4, 7.9 Hz, 1H), 2.69 - 2.61 (m, 2H), 2.39 - 2.26 (m, 2H), 1.91 (d, J=15.0 Hz, 1H), 1.85 (d, J=6.1 Hz, 1H), 1.70 (dd, J=13.1, 7.0 Hz, 1H), 1.58 - 1.49 (m, 4H), 1.42 (br. s., 1H), 1.40 - 1.36 (m, 4H),

1.30 - 1.20 (m, 2H), 1.15 (d, J=12.5 Hz, 1H), 1.11 (s, 3H), 0.94 (d, J=6.7 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.76 (t, J=12.8 Hz, 1H). MS: MS *m/z* 908.45 (M^++1).

Preparation of Compounds 1170 and 1171



Compound 1170



Compound 1171

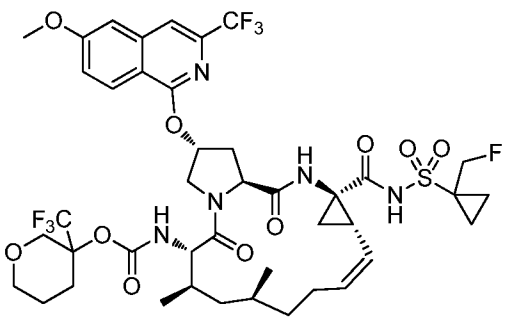
Compounds 1170 and 1171 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1170: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxy-3-(trifluoromethyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 904.5 (M^++1).

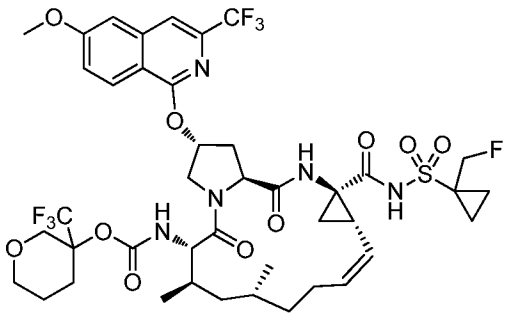
Compound 1171: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxy-3-(trifluoromethyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.27 (s, 1H), 9.00 (s, 1H), 8.11 (d, J=9.2 Hz, 1H), 7.93 (s, 1H), 7.63 (d, J=8.2 Hz, 1H), 7.60 (d, J=2.4 Hz, 1H), 7.33 (dd, J=9.3, 2.3 Hz, 1H), 5.82 (br. s., 1H), 5.54 - 5.49 (m, 1H), 5.02 (t, J=9.5 Hz, 1H), 4.90 - 4.71 (m, 1H), 4.59 (t, J=10.5 Hz, 2H),

4.52 - 4.47 (m, 1H), 3.95 (br. s., 1H), 3.94 (s, 3H), 3.72 - 3.68 (m, 1H), 3.18 (d, J=5.2 Hz, 1H), 2.71 - 2.61 (m, 2H), 2.39 - 2.27 (m, 2H), 1.93 - 1.87 (m, 1H), 1.82 (d, J=6.7 Hz, 1H), 1.72 - 1.66 (m, 1H), 1.62 (s, 1H), 1.58 (s, 1H), 1.56 (br. s., 1H), 1.54 (br. s., 3H), 1.44 (br. s., 1H), 1.37 (br. s., 1H), 1.28 (s, 3H), 1.23 (br. s., 2H), 1.21 - 1.13 (m, 1H), 1.01 (s, 3H), 0.94 (d, J=7.0 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.77 (t, J=12.7 Hz, 1H). MS: MS *m/z* 904.5 (M^++1).

Preparation of Compound 1172 and 1173



Compound 1172



Compound 1173

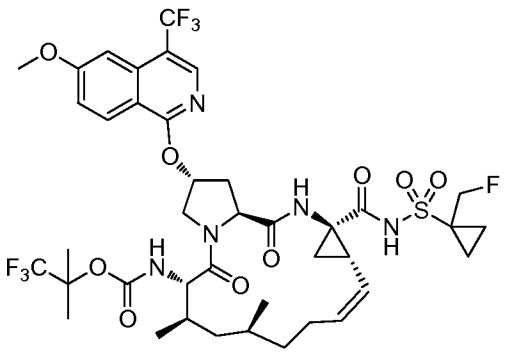
Compounds 1172 and 1173 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1172: 3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxy-3-(trifluoromethyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 950.5 (M^++1).

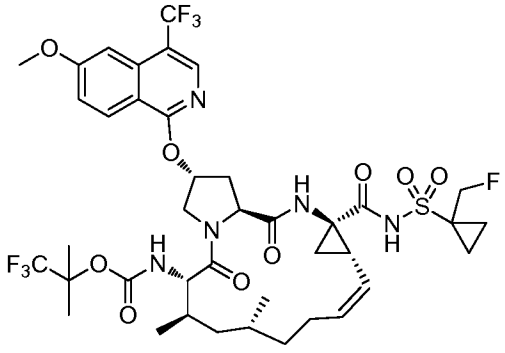
Compound 1173: 3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxy-3-(trifluoromethyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-

a][1,4]diazacyclopentadecin-6-yl)carbamate. *Diastereomer 1 HNMR:* 1H NMR (500MHz, DMSO-d6) Shift 11.26 (s, 1H), 9.01 (s, 1H), 8.08 (d, J=9.2 Hz, 1H), 7.97 (d, J=8.2 Hz, 1H), 7.93 (s, 1H), 7.60 (d, J=2.4 Hz, 1H), 7.29 (dd, J=9.2, 2.4 Hz, 1H), 5.82 (br. s., 1H), 5.55 - 5.49 (m, 1H), 5.02 (t, J=9.6 Hz, 1H), 4.86 (d, J=11.3 Hz, 1H), 4.64 - 4.38 (m, 3H), 4.15 - 4.10 (m, 1H), 3.97 (d, J=11.3 Hz, 1H), 3.94 (s, 3H), 3.77 - 3.72 (m, 1H), 3.56 (d, J=11.0 Hz, 1H), 3.49 (d, J=11.6 Hz, 1H), 3.40 (t, J=10.7 Hz, 1H), 2.70 - 2.60 (m, 2H), 2.38 - 2.27 (m, 2H), 2.14 - 2.08 (m, 1H), 1.90 (d, J=19.5 Hz, 2H), 1.77 - 1.68 (m, 2H), 1.58 - 1.50 (m, 5H), 1.43 (br. s., 1H), 1.41 - 1.29 (m, 2H), 1.29 - 1.20 (m, 2H), 1.20 - 1.10 (m, 1H), 0.94 (d, J=6.7 Hz, 3H), 0.91 (d, J=6.4 Hz, 3H), 0.77 (t, J=13.1 Hz, 1H) . *Diastereomer 2 HNMR:* 1H NMR (500MHz, DMSO-d6) Shift 11.25 (s, 1H), 8.97 (s, 1H), 8.10 (d, J=9.2 Hz, 1H), 7.95 (d, J=7.9 Hz, 1H), 7.93 (s, 1H), 7.59 (d, J=2.1 Hz, 1H), 7.29 (dd, J=8.9, 2.4 Hz, 1H), 5.80 (br. s., 1H), 5.52 (d, J=6.4 Hz, 1H), 5.03 (t, J=10.1 Hz, 1H), 4.76 (d, J=11.3 Hz, 1H), 4.61 - 4.42 (m, 3H), 4.10 (d, J=13.1 Hz, 1H), 3.96 (br. s., 1H), 3.94 (s, 3H), 3.79 - 3.74 (m, 1H), 3.59 (d, J=11.0 Hz, 1H), 3.49 (d, J=11.9 Hz, 1H), 3.44 - 3.39 (m, 1H), 2.71 - 2.60 (m, 2H), 2.39 - 2.26 (m, 2H), 2.16 (d, J=12.2 Hz, 1H), 1.96 - 1.83 (m, 2H), 1.83 - 1.76 (m, 1H), 1.75 - 1.63 (m, 2H), 1.53 (br. s., 3H), 1.44 (br. s., 2H), 1.36 (d, J=17.7 Hz, 1H), 1.24 (d, J=15.0 Hz, 2H), 1.21 - 1.09 (m, 2H), 0.94 (d, J=6.7 Hz, 3H), 0.92 (d, J=6.1 Hz, 3H), 0.77 (t, J=12.7 Hz, 1H). MS: MS *m/z* 950.5 (M^++1).

Preparation of Compounds 1174 and 1175



Compound 1174



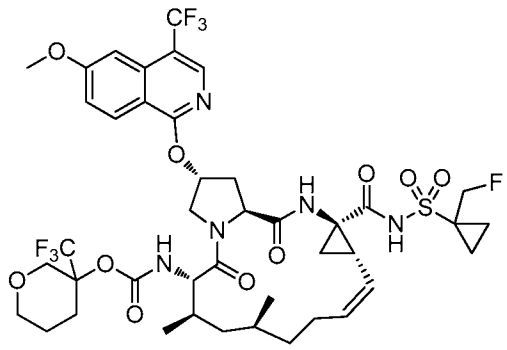
Compound 1175

Compounds 1174 and 1175 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

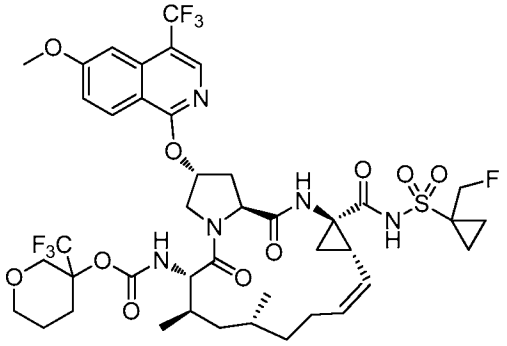
Compound 1174: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxy-4-(trifluoromethyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 908.45 (M^++1).

Compound 1175: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxy-4-(trifluoromethyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, METHANOL-d4) Shift 8.36 (s, 1H), 8.24 (d, J=9.2 Hz, 1H), 7.30 (s, 1H), 7.26 (dd, J=9.2, 2.4 Hz, 1H), 5.91 (br. s., 1H), 5.57 (td, J=10.0, 5.6 Hz, 1H), 5.13 (br. s., 1H), 4.86 - 4.74 (m, 2H), 4.68 - 4.58 (m, 2H), 4.02 (dd, J=11.7, 3.2 Hz, 1H), 3.96 (s, 3H), 3.77 (d, J=10.7 Hz, 1H), 2.76 (dd, J=14.0, 7.0 Hz, 1H), 2.62 (q, J=8.9 Hz, 1H), 2.48 (ddd, J=14.1, 10.3, 4.0 Hz, 1H), 2.43 - 2.32 (m, 1H), 1.99 - 1.89 (m, 1H), 1.89 - 1.82 (m, 1H), 1.82 - 1.74 (m, 1H), 1.70 (dd, J=8.4, 5.3 Hz, 1H), 1.68 - 1.59 (m, 2H), 1.56 (dd, J=9.5, 5.2 Hz, 1H), 1.51 - 1.39 (m, 2H), 1.29 (s, 3H), 1.28 - 1.08 (m, 3H), 1.00 (d, J=7.0 Hz, 3H), 0.97 (d, J=6.4 Hz, 3H), 0.87 (s, 3H), 0.81 (t, J=11.4 Hz, 1H). MS: MS *m/z* 908.45 (M^++1).

Preparation of Compounds 1176 and 1177



Compound 1176



Compound 1177

Compounds 1176 and 1177 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

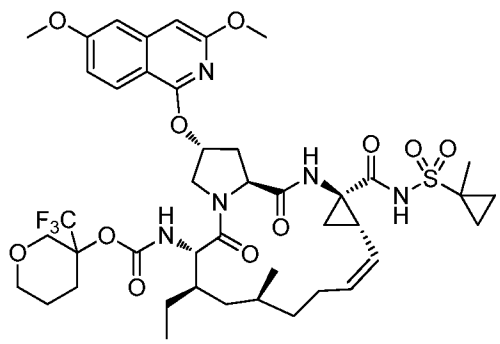
Compound 1176: 3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxy-4-(trifluoromethyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 950.5 (M^++1).

Compound 1177: 3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxy-4-(trifluoromethyl)isoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. *Diastereomer 1 HNMR:* 1H NMR (500MHz, METHANOL-d4) Shift 8.34 (s, 1H), 8.23 (d, J=9.2 Hz, 1H), 7.29 (s, 1H), 7.24 (dd, J=9.2, 2.1 Hz, 1H), 5.92 (br. s., 1H), 5.57 (td, J=10.1, 5.6 Hz, 1H), 5.10 (br. s., 1H), 4.79 - 4.75 (m, 2H), 4.65 - 4.57 (m, 2H), 4.54 (d, J=11.0 Hz, 1H), 4.16 - 4.10 (m, 1H), 4.04 (dd, J=11.6, 3.4 Hz, 1H), 3.96 (s, 3H), 3.83 (d, J=10.7 Hz, 1H), 3.63 - 3.56 (m, 1H), 3.42 - 3.33 (m, 2H), 2.75 (dd, J=14.0, 7.0 Hz, 1H), 2.65 (q, J=8.9 Hz,

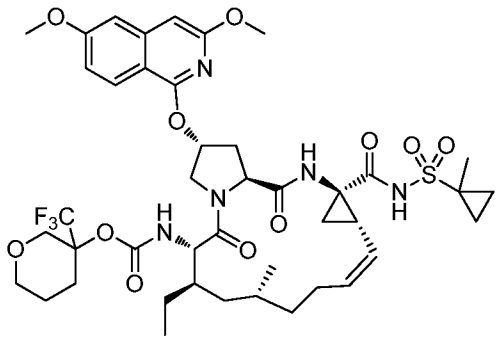
1H), 2.47 (ddd, J=14.0, 10.2, 4.1 Hz, 1H), 2.44 - 2.34 (m, 1H), 2.06 (d, J=15.0 Hz, 1H), 1.99 - 1.85 (m, 2H), 1.81 (dd, J=13.3, 6.0 Hz, 1H), 1.72 - 1.67 (m, 1H), 1.67 - 1.60 (m, 3H), 1.59 - 1.51 (m, 2H), 1.50 - 1.41 (m, 2H), 1.33 - 1.27 (m, 1H), 1.27 - 1.18 (m, 2H), 1.18 - 1.12 (m, 1H), 1.01 (t, J=5.8 Hz, 6H), 0.83 (t, J=11.7 Hz, 1H).

Diastereomer 2 HNMR: 1H NMR (500MHz, METHANOL-d4) Shift 8.33 (s, 1H), 8.23 (d, J=9.2 Hz, 1H), 7.29 (s, 1H), 7.25 (dd, J=9.2, 2.4 Hz, 1H), 5.94 - 5.90 (m, 1H), 5.55 (td, J=10.1, 5.8 Hz, 1H), 5.03 (br. s., 1H), 4.80 - 4.70 (m, 2H), 4.64 - 4.58 (m, 2H), 4.52 (d, J=11.3 Hz, 1H), 4.05 (ddd, J=11.7, 5.6, 2.7 Hz, 2H), 3.96 (s, 3H), 3.87 (d, J=11.0 Hz, 1H), 3.61 (d, J=10.1 Hz, 1H), 3.39 - 3.33 (m, 1H), 2.75 (dd, J=13.9, 6.9 Hz, 1H), 2.67 (q, J=9.1 Hz, 1H), 2.45 (ddd, J=14.1, 10.3, 4.0 Hz, 1H), 2.42 - 2.34 (m, 1H), 2.21 (br. s., 1H), 1.93 - 1.82 (m, 2H), 1.82 - 1.74 (m, 1H), 1.74 - 1.67 (m, 3H), 1.67 - 1.60 (m, 2H), 1.54 (dd, J=9.5, 5.5 Hz, 1H), 1.49 (br. s., 1H), 1.45 - 1.35 (m, 2H), 1.25 - 1.14 (m, 3H), 1.00 (t, J=6.6 Hz, 6H), 0.83 (t, J=11.6 Hz, 1H). MS: MS *m/z* 950.5 (M^++1).

Preparation of Compounds 1178 and 1179



Compound 1178



Compound 1179

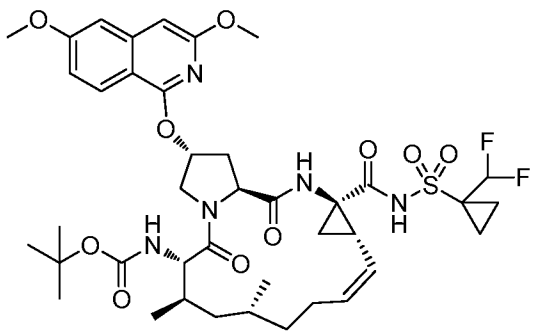
Compounds 1178 and 1179 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1178: 3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 908.8 (M^++1).

Compound 1179: 3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. *Diastereomer 1:* 1H NMR (500MHz, METHANOL-d4) Shift 7.93 (d, J=8.9 Hz, 1H), 7.04 - 6.97 (m, 1H), 6.84 (dd, J=9.2, 2.1 Hz, 1H), 6.55 (s, 1H), 5.85 (br. s., 1H), 5.62 - 5.55 (m, 1H), 5.06 (br. s., 1H), 4.71 (d, J=11.3 Hz, 1H), 4.60 (dd, J=9.6, 7.2 Hz, 1H), 4.17 - 4.12 (m, 2H), 4.07 (dd, J=11.4, 3.5 Hz, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.59 (d, J=11.3 Hz, 1H), 3.45 (d, J=11.9 Hz, 1H), 3.44 - 3.38 (m, 1H), 2.78 - 2.66 (m, 2H), 2.48 - 2.40 (m, 2H), 2.27 (d, J=14.0 Hz, 1H), 2.05 - 1.92 (m, 2H), 1.77 - 1.70 (m, 2H), 1.66 - 1.52 (m, 3H), 1.51 (s, 3H), 1.46 (br. s., 2H), 1.41 (dd, J=9.6, 5.3 Hz, 2H), 1.34 - 1.21 (m, 2H), 1.12 (t, J=13.1 Hz, 1H), 1.00 (d, J=7.0 Hz, 3H), 0.85 (t, J=7.3 Hz, 6H), 0.79 (d, J=8.2 Hz, 1H). *Diastereomer 2:* 1H NMR (500MHz, METHANOL-d4) Shift 7.94 (d, J=9.2 Hz, 1H), 7.01 (d, J=2.4 Hz, 1H), 6.85 (dd, J=9.0, 2.3 Hz, 1H), 6.55 (s, 1H), 5.84 (br. s., 1H), 5.62 - 5.49 (m, 1H), 5.05 (br. s., 1H), 4.70 (d, J=11.6 Hz, 1H), 4.56 (dd, J=9.8, 7.3 Hz, 1H), 4.20 - 4.13 (m, 2H), 4.10 - 4.06 (m, 1H), 3.99 - 3.92 (m, 3H), 3.90 (s, 3H), 3.70 - 3.65 (m, 1H), 3.53 (d, J=11.9 Hz, 1H), 3.48 - 3.42 (m, 1H), 2.76 (dd, J=13.9, 7.2 Hz, 1H), 2.67 (br. s., 1H), 2.43 (ddd, J=13.9, 9.9, 4.3 Hz, 2H), 2.35 (d, J=13.7 Hz, 1H), 2.00 (t, J=11.4 Hz, 1H), 1.96 - 1.90 (m, 1H), 1.90 - 1.70 (m, 2H), 1.67 - 1.50 (m, 3H), 1.49 (s, 3H), 1.43 - 1.34 (m, 3H), 1.34 - 1.27 (m, 1H), 1.26 - 1.08 (m, 3H), 0.98 (d, J=7.0 Hz, 3H), 0.86 (t, J=7.5 Hz, 6H), 0.78 (d, J=7.9 Hz, 1H). MS: MS *m/z* 908.8 (M^++1).

Preparation of Compound 1180

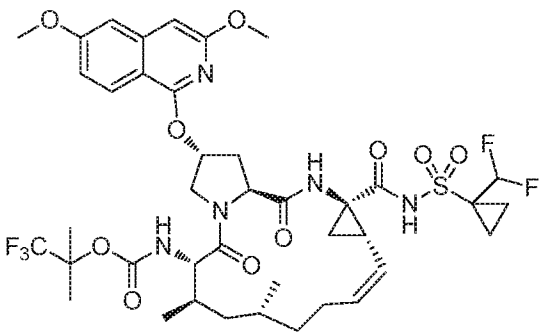


Compound 1180

Compound 1180 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1180: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(difluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.53 (s, 1H), 9.00 (s, 1H), 7.92 (d, J=9.2 Hz, 1H), 7.21 (d, J=7.6 Hz, 1H), 7.14 (s, 1H), 6.86 (dd, J=9.2, 2.1 Hz, 1H), 6.63 - 6.61 (m, 1H), 6.60 - 6.33 (m, 1H), 5.76 (br. s., 1H), 5.51 (d, J=6.7 Hz, 1H), 5.03 (t, J=9.8 Hz, 1H), 4.58 (d, J=10.7 Hz, 1H), 4.45 - 4.40 (m, 1H), 3.95 - 3.91 (m, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.76 - 3.71 (m, 1H), 2.73 - 2.60 (m, 2H), 2.34 - 2.25 (m, 2H), 1.92 (d, J=8.2 Hz, 1H), 1.82 (br. s., 1H), 1.69 (br. s., 1H), 1.56 (d, J=8.2 Hz, 4H), 1.43 (br. s., 1H), 1.37 (br. s., 3H), 1.21 (s, 9H), 1.16 (d, J=13.7 Hz, 1H), 1.09 (br. s., 1H), 0.93 (d, J=6.7 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H), 0.74 (t, J=11.6 Hz, 1H). MS: MS *m/z* 834.6 (M^++1).

Preparation of Compound 1181

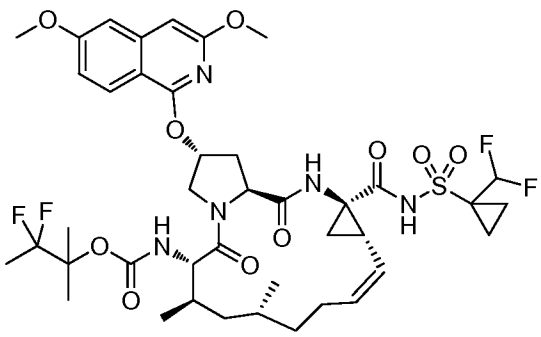


Compound 1181

Compound 1181 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1181: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(difluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.52 (s, 1H), 9.04 (s, 1H), 7.89 (d, J=9.2 Hz, 1H), 7.85 (d, J=7.6 Hz, 1H), 7.16 (d, J=1.8 Hz, 1H), 6.90 (dd, J=8.9, 2.1 Hz, 1H), 6.63 (s, 1H), 6.60 - 6.35 (m, 1H), 5.77 (br. s., 1H), 5.52 (d, J=6.7 Hz, 1H), 5.04 (t, J=9.9 Hz, 1H), 4.53 (d, J=11.6 Hz, 1H), 4.49 - 4.45 (m, 1H), 3.96 - 3.91 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.75 - 3.71 (m, 1H), 2.69 - 2.61 (m, 2H), 2.35 - 2.27 (m, 2H), 1.92 (s, 1H), 1.85 (d, J=5.8 Hz, 1H), 1.69 (br. s., 1H), 1.58 (d, J=5.2 Hz, 4H), 1.50 - 1.45 (m, 1H), 1.41 (s, 3H), 1.37 (br. s., 3H), 1.20 (s, 3H), 1.15 (br. s., 1H), 0.93 (d, J=7.0 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.75 (t, J=12.8 Hz, 1H). MS: MS *m/z* 888.5 (M^++1).

Preparation of Compound 1182

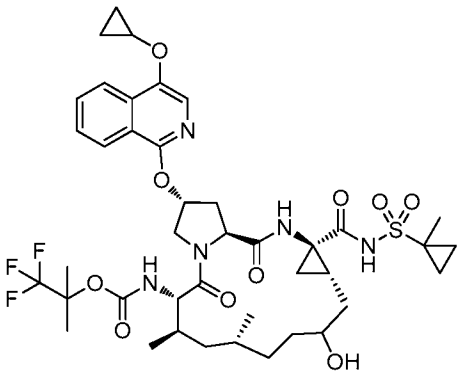


Compound 1182

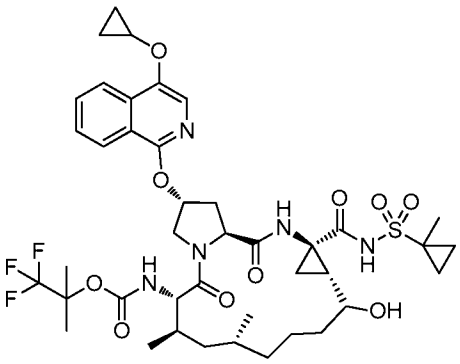
Compound 1182 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 1182: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(difluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. 1H NMR (500MHz, DMSO-d6) Shift 11.53 (s, 1H), 9.01 (s, 1H), 7.89 (d, J=9.2 Hz, 1H), 7.64 (d, J=8.2 Hz, 1H), 7.16 (d, J=2.1 Hz, 1H), 6.89 (dd, J=9.0, 2.3 Hz, 1H), 6.63 (s, 1H), 6.60 - 6.34 (m, 1H), 5.77 (br. s., 1H), 5.52 (d, J=6.1 Hz, 1H), 5.04 (t, J=10.1 Hz, 1H), 4.53 (d, J=11.0 Hz, 1H), 4.48 - 4.43 (m, 1H), 3.96 - 3.91 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.76 - 3.72 (m, 1H), 2.71 (d, J=9.2 Hz, 1H), 2.64 (d, J=11.0 Hz, 1H), 2.35 - 2.26 (m, 2H), 1.92 (d, J=8.2 Hz, 1H), 1.83 (d, J=6.1 Hz, 1H), 1.68 (br. s., 1H), 1.64 (s, 1H), 1.61 - 1.54 (m, 6H), 1.45 (br. s., 1H), 1.37 (br. s., 3H), 1.32 (s, 3H), 1.21 - 1.14 (m, 1H), 1.12 (s, 3H), 0.94 (d, J=6.7 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.76 (t, J=12.2 Hz, 1H). MS: MS *m/z* 884.5 (M^++1).

Preparation of Compound 2001 and Compound 2002



Compound 2001



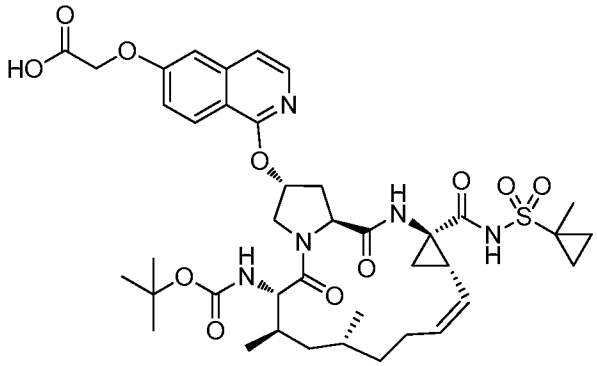
Compound 2002

To a 2 dram vial equipped with a stir bar was added 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-cyclopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate, Compound 4056 (200 mg, 0.236 mmol) and THF (0.8 mL). The solution was cooled to 0 °C. To the stirred solution was added borane in THF (0.7 mL, 1.0 M). The solution was allowed to warm to room temperature with stirring for 1h. The solution was cooled to 0 °C and to the solution was added potassium acetate (225 mg, 2.29 mmol). To the solution was added dropwise hydrogen peroxide (0.75 mL, 30% wt. aq.). The mixture was allowed to warm to room temperature with stirring for 17h. The mixture was transferred to a 125 mL separatory funnel and was diluted with EtOAc (50 mL). The organic solution was washed with water:brine (15 mL:15 mL); dried over MgSO4; filtered; then concentrated in vacuo. The resulting residue was subjected to HPLC purification as follows: Column = Waters XBridge C18, 19 x 200 mm, 5-μmparticles; Guard Column = Waters XBridge C18, 19 x 10 mm, 5-μm particles; Mobile Phase A = water with 20-mM ammonium acetate;Mobile Phase B = 95:5 acetonitrile:water with 20-mM ammonium acetate; Gradient = 55-95% B over 12 minutes, then a 5-minute hold at 100% B; Flow = 20 mL/min. The appropriate fractions were combined and dried via centrifugal evaporation to afford Compound 2001 (30 mg, 15%). The appropriate fractions were combined and dried via centrifugal evaporation to afford Compound 2002 (13 mg, 6%); Compound 2001: 1,1,1-trifluoro-2-

methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS)-2-((4-cyclopropoxyisoquinolin-1-yl)oxy)-12-hydroxy-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400MHz, MeOD) δ 8.14 (d, *J*=8.3 Hz, 1H), 8.01 (d, *J*=8.3 Hz, 1H), 7.87 (s, 1H), 7.70 (ddd, *J*=8.3, 7.0, 1.3 Hz, 1H), 7.54 (ddd, *J*=8.2, 7.1, 1.0 Hz, 1H), 5.83 - 5.78 (m, 1H), 4.74 (d, *J*=11.0 Hz, 1H), 4.60 (dd, *J*=10.2, 6.9 Hz, 1H), 4.02 - 3.95 (m, 2H), 3.81 (d, *J*=10.8 Hz, 1H), 3.66 (br. s., 1H), 2.74 (dd, *J*=13.7, 6.9 Hz, 1H), 2.39 (ddd, *J*=13.8, 10.2, 4.1 Hz, 1H), 2.02 (q, *J*=9.5 Hz, 1H), 1.90 - 1.78 (m, 1H), 1.76 - 1.65 (m, 3H), 1.63 - 1.51 (m, 6H), 1.51 - 1.48 (m, 1H), 1.47 - 1.42 (m, 2H), 1.41 - 1.34 (m, 2H), 1.33 (s, 3H), 1.20 - 1.09 (m, 1H), 1.00 (d, *J*=6.8 Hz, 3H), 0.95 (d, *J*=6.5 Hz, 3H), 0.93 - 0.86 (m, 7H), 0.84 - 0.80 (m, 2H), 0.80 - 0.73 (m, 1H); MS: MS *m/z* 866.4 (M^++1).

Compound 2002: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13S,13aR,14aR,16aS)-2-((4-cyclopropoxyisoquinolin-1-yl)oxy)-13-hydroxy-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxooctadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400MHz, MeOD) δ 8.16 (d, *J*=8.3 Hz, 1H), 8.03 (d, *J*=8.3 Hz, 1H), 7.90 - 7.86 (m, 1H), 7.72 (ddd, *J*=8.3, 7.1, 1.1 Hz, 1H), 7.55 (td, *J*=7.7, 1.0 Hz, 1H), 5.82 (br. s., 1H), 4.77 (d, *J*=11.3 Hz, 1H), 4.62 (dd, *J*=10.2, 6.9 Hz, 1H), 4.05 - 3.96 (m, 2H), 3.84 - 3.78 (m, 1H), 3.69 (d, *J*=6.0 Hz, 1H), 2.76 (dd, *J*=13.6, 7.0 Hz, 1H), 2.41 (ddd, *J*=13.7, 10.1, 4.0 Hz, 1H), 1.99 - 1.89 (m, 1H), 1.85 - 1.60 (m, 7H), 1.58 (s, 3H), 1.54 - 1.40 (m, 4H), 1.34 (s, 3H), 1.30 - 1.19 (m, 1H), 1.17 - 1.08 (m, 1H), 1.06 (d, *J*=6.8 Hz, 3H), 0.99 (d, *J*=6.5 Hz, 3H), 0.97 - 0.87 (m, 7H), 0.87 - 0.82 (m, 2H), 0.82 - 0.75 (m, 1H); MS: MS *m/z* 866.4 (M^++1).

Preparation of Compound 2003



Compound 2003

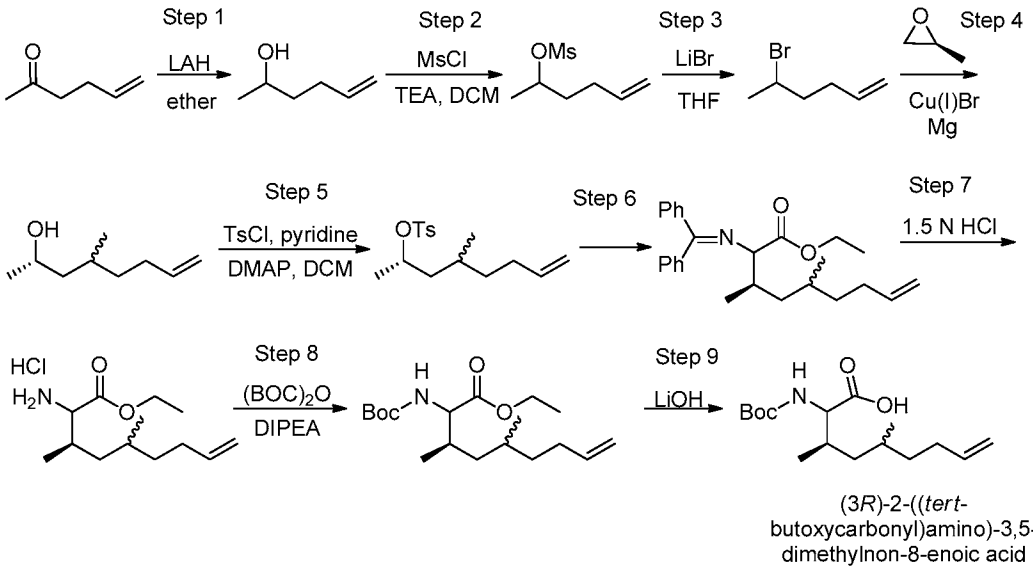
Compound 2003 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117.

Compound 2003: 2-((1-(((2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-((tert-butoxycarbonyl)amino)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-2-yl)oxy)isoquinolin-6-yl)oxy)acetic acid. ^{1}H NMR (500MHz, DMSO-d_6) δ 9.05 (br. s., 1H), 8.05 (d, *J*=9.2 Hz, 1H), 7.93 (d, *J*=5.8 Hz, 1H), 7.27 (d, *J*=5.8 Hz, 1H), 7.23 (d, *J*=2.4 Hz, 1H), 7.18 (d, *J*=7.9 Hz, 1H), 7.13 (dd, *J*=9.2, 2.4 Hz, 1H), 5.80 (br. s., 1H), 5.55 - 5.47 (m, 1H), 4.97 (t, *J*=9.8 Hz, 1H), 4.78 (s, 2H), 4.59 (d, *J*=11.0 Hz, 1H), 4.46 (dd, *J*=10.4, 7.0 Hz, 1H), 3.93 - 3.87 (m, 1H), 3.74 - 3.68 (m, 1H), 2.72 - 2.62 (m, 1H), 2.59 (dd, *J*=13.4, 7.0 Hz, 1H), 2.38 - 2.23 (m, 3H), 1.93 - 1.77 (m, 2H), 1.68 (dd, *J*=12.7, 6.3 Hz, 1H), 1.58 (dd, *J*=8.1, 5.3 Hz, 1H), 1.49 (dd, *J*=9.3, 5.0 Hz, 1H), 1.45 - 1.23 (m, 8H), 1.14 (s, 9H), 0.92 (d, *J*=7.0 Hz, 3H), 0.89 - 0.85 (m, 4H), 0.72 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 812.4 (M^++1).

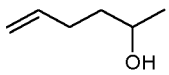
Preparation of intermediates and Compounds of Formula 1

Section 3

Scheme: Preparation of (3R)-2-((tert-butoxycarbonyl) amino)-3, 5-dimethylnon-8-enoic acid

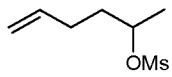


Step 1: Preperation of *Hex-5-en-2-ol*



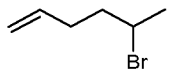
To a solution of lithium alliuminum hydride in THF (LAH, 20.1 g, 106.12 mmol, 509 mL, 1M solution) was added a solution of Hex-5-en-2-one (50 g, 102.04 mmol) over a period of 30 min. at -20 °C under nitrogen. The reaction mass was allowed to warm to room temperature and stirred for 1 h. The solution was cooled to -20 °C and to it was added aqueous 10% NaOH solution (~100 mL). The organic layer was separated and the aqueous layer was extracted with ether. The combined organics were dried over anhydrous sodium sulfate and concentrated to get crude compound *Hex-5-en-2-ol* as colorless liquid (50 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 5.87-5.02 (m, 1 H), 4.99-4.95 (m, 2 H), 3.81-3.83 (m, 1 H), 2.17-2.13 (m, 2 H), 1.58-1.53 (m, 2 H), 1.20-1.19 (d, *J*= 8 Hz, 3 H).

Step 2: Preperation of *Hex-5-en-2-yl methanesulfonate*



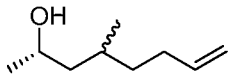
To a solution of *Hex-5-en-2-ol* (50 g crude, 500 mmole) in dichloromethane was added triethylamine (103 mL, 750 mmol) at room temperature. The reaction mass was cooled to 0 °C and to it was added a solution of methane sulfonyl chloride (50.4 mL, 650 mmol) in DCM over a period of 30 min. The reaction mass was allowed to come to room temperature and stirred for 2 h. The solution was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude compound *Hex-5-en-2-yl methanesulfonate* as light brown oily liquid (73 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 5.84-5.80 (m, 1 H), 5.10-5.0 (m, 2 H), 4.99-4.98 (m, 1 H), 3.15 (s, 3H), 2.52-2.09 (m, 2 H), 1.75-1.66 (m, 2 H), 1.36-1.34 (d, *J*= 6.4 Hz, 3 H).

Step 3: Preperation of *5-bromohex-1-ene*



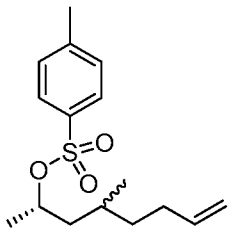
To a solution of *Hex-5-en-2-yl methanesulfonate* (20 g, 0.112 moles) in dry THF (200 mL) was added LiBr (14.6 g, 0.168 moles) portionwise at room temperature over a period of 15 min. The reaction mass was heated at 70 °C for 3 h. The reaction mass was cooled to room temperature and was diluted with water (200 mL). The aqueous solution was extracted with ether (100 mL x 3). The combined organics were dried over anhydrous Na_2SO_4 and concentrated at room temperature. The crude compound was distilled under reduced pressure at 115 °C to afford 5-bromohex-1-ene as colorless liquid (14.5 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 5.80-5.74 (m, 1 H), 5.08-4.98 (m, 2 H), 4.14-4.09 (m, 1 H), 2.28-2.17 (m, 2 H), 1.94-1.81 (m, 2 H), 1.71-1.70 (d, *J*= 6.8 Hz, 3 H); MS: GC-MS *m/z* 162.

Step 4: Preperation of *(2S)-4-methyloct-7-en-2-ol*



To magnesium turnings (7.44 g, 0.020 moles) in dry THF (100 mL) and was added a iodine (100 mg) at room temperature. To this reaction mass was added a solution of *5-bromohex-1-ene* (50 g, 362 mmoles) in THF (200 mL). The reaction mass was heated with hot air gun to initiate the reaction. Upon completion of the reaction the solution was transferred by cannula to a solution of (S)-propylene oxide (14 g, 241 mmol) and copper bromide (3.45 g, 24 mmol) in THF (100 mL) at -78 °C. The reaction mass was allowed to come to room temperature and was stirred overnight. The reaction mass was quenched with saturated aq. ammonium chloride solution and extracted with diethyl ether (200 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated at room temperature to get crude compound. The crude compound was purified by column chromotography (Silica gel, 10% TBME in pet ether) to get *(2S)-4-methyloct-7-en-2-ol* (12.4 g, 30%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 5.84-5.77 (m, 1 H), 5.02-4.92 (m, 2 H), 4.05-3.85 (s*b*, 1 H), 2.08-2.06 (m, 2 H), 1.29-1.20 (m, 2 H), 1.19-1.16 (m, 4 H), 0.97-0.87 (m, 6 H).

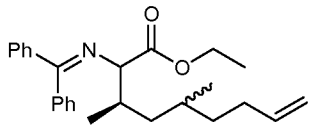
Step 5: Preperation of *(2S)-4-methyloct-7-en-2-yl 4-methylbenzenesulfonate*



To a solution of *(2S)-4-methyloct-7-en-2-ol* (39 g, 0.274 moles) in pyridine (400 mL) was added 4-(dimethylamino)pyridine (DMAP, 1.67 g, 0.013 moles) and the solution was stirred for 10 min. P-toluenesulfonyl chloride (60 g, 0.315 moles) was added to the reaction mass at 0 °C. The reaction mass was allowed to come to room temperature and stirred overnight. Pyridine was removed under reduced pressure and the residue was diluted with ethyl acetate (200 mL). The organic

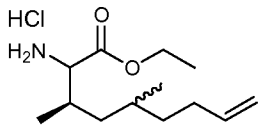
solution was washed with aqueous 1.5 N HCl solution, saturated aq. bicarbonate solution, brine solution, dried over anhydrous Na_2SO_4, filter, and concentrated under reduced pressure to get crude compound *(2S)-4-methyloct-7-en-2-yl 4-methylbenzenesulfonate* (54 g, 61%). The crude compound was taken to the next step without further purification.

Step 6: Preperation of *(3R)-ethyl 2-((diphenylmethylene) amino)-3, 5-dimethylnon-8-enoate*



To a solution of *(2S)-4-methyloct-7-en-2-yl 4-methylbenzenesulfonate* (54 g, 0.182 moles) and *N*-(diphenylmethylene)glycinate ethyl ester (48.7 g, 0.182 moles) in toluene (500 mL) was added LiHMDS (36.5 g, 0.218 moles, 1 M solution in THF) at 0 °C. The reaction mass was allowed to come to room temperature and was then heated at 110 °C for 2 h. The reaction mass was cooled to room temperature, quenched with water and extracted with ethyl acetate (200 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound (3R)-ethyl 2-((diphenylmethylene) amino)-3, 5-dimethylnon-8-enoate (75 g). The crude compound was taken to the next step without further purification.

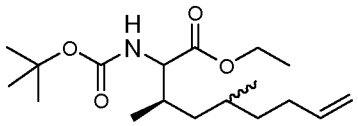
Step 7: Preperation of *(3R)-ethyl 2-amino-3,5-dimethylnon-8-enoate hydrochloride*



To a solution of (3R)-ethyl 2-((diphenylmethylene) amino)-3, 5-dimethylnon-8-enoate (20 g) in diethyl ether (20 mL) was added aqueous 1.5 N HCl solution (200 mL) and the reaction mass was stirred at room temperature overnight. The reaction mass was washed with diethyl ether (100 mL). The aqueous solution was basified using saturated sodium bicarbonate solution and was extracted with ethyl acetate (100

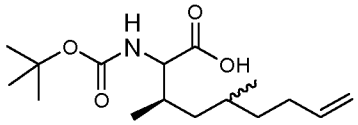
mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude compound *(3R)-ethyl 2-amino-3,5-dimethylnon-8-enoate hydrochloride* (4 g, 30%). The crude compound was taken to the next step without further purification.

Step 8: Preperation of *(3R)-ethyl 2-(tert-butoxycarbonylamino)-3,5-dimethylnon-8-enoate*



A solution of *(3R)-ethyl 2-amino-3,5-dimethylnon-8-enoate hydrochloride* (4 g, 0.017 moles) in DCM (40 mL) was added N,N-diisopropylethylamine (DIPEA, 3.4 g, 0.026 moles) followed by di-tert-butyl dicarbonate (4.6 g, 0.021 moles) at room temperature. The reaction mass was stirred at room temperature overnight. The reaction mass was diluted with DCM and washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude compound. The crude compound was purified by column chromotography (Silica gel, 20% ethyl acetate in pet-ether) to get 4.7 g, (94%) of (3R)-ethyl 2-(tert-butoxycarbonylamino)-3,5-dimethylnon-8-enoate as an oil.

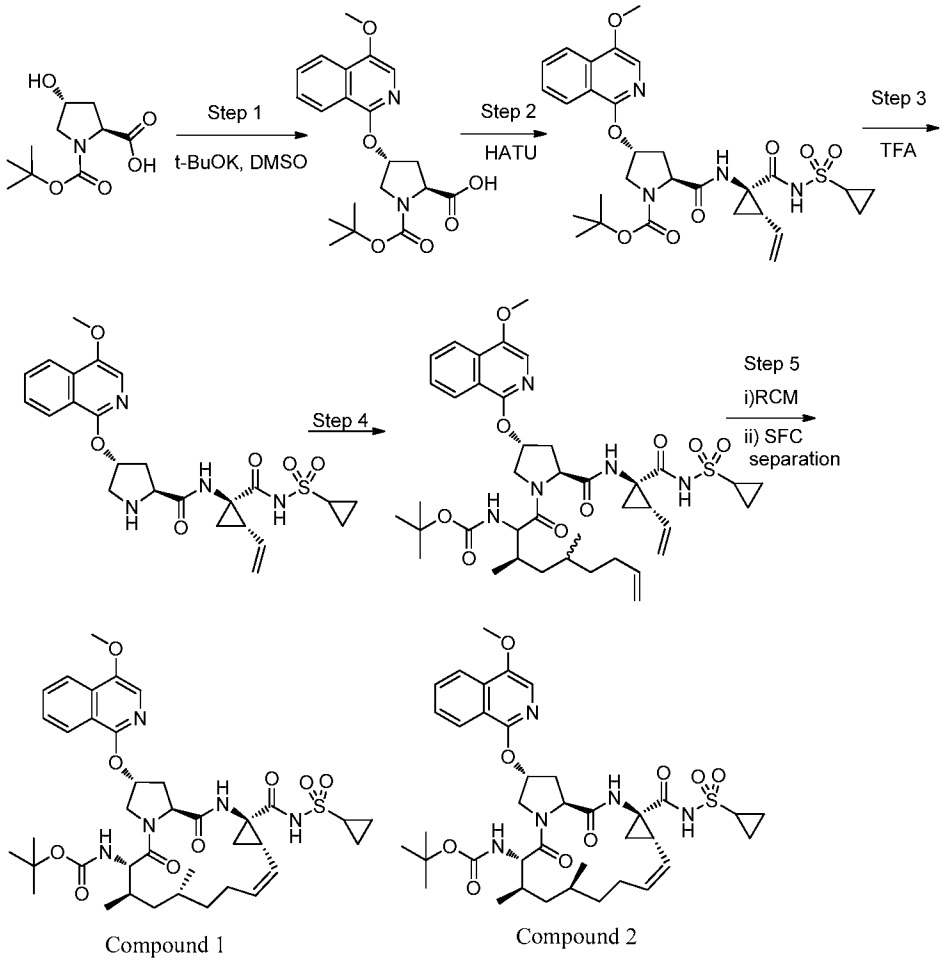
Step 9: Preperation of *(3R)-2-(tert-butoxycarbonylamino)-3,5-dimethylnon-8-enoic acid*



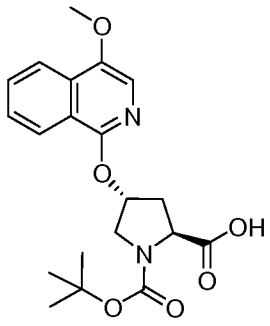
To a solution of (3R)-ethyl 2-(tert-butoxycarbonylamino)-3,5-dimethylnon-8-enoate (20 g, 0.061 moles) in THF/water (200 mL, 1: 1) was added methanol (60 mL) followed by LiOH (7.7 g, 0.183 moles) at room temperature. The reaction mass was stirred at room temperature overnight. The solution was concentrated under reduced pressure and the residue was diluted with water (200 mL). The aqueous solution was acidified with aqueous 1.5 N HCl solution to pH ~3 and extracted with ethyl acetate (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and

concentrated under reduce pressure to get crude compound. The crude compound was purified by column chromotography (Silica gel, 3% methanol in DCM) to get 12.4 g (68%) of *(3R)-2-(tert-butoxycarbonylamino)-3,5-dimethylnon-8-enoic acid* as gummy liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.4 (s*b*, 1 H), 6.92-6.85 (m, 1 H), 5.81-5.75 (m, 1 H), 5.04-4.93 (m, 2 H), 4.12-3.91 (m, 1 H), 2.18-1.98 (m, 4 H), 1.5 (s, 9H), 1.35-1.02 (m, 3 H), 0.98-0.85 (m, 6 H).

Scheme

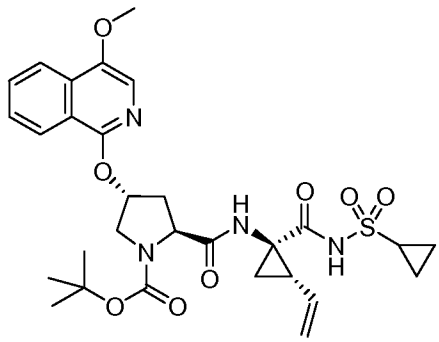


Step 1: Preperation of *(2S,4R)-1-(tert-butoxycarbonyl)-4-((4-methoxyisoquinolin-1-yl)oxy)pyrrolidine-2-carboxylic acid*



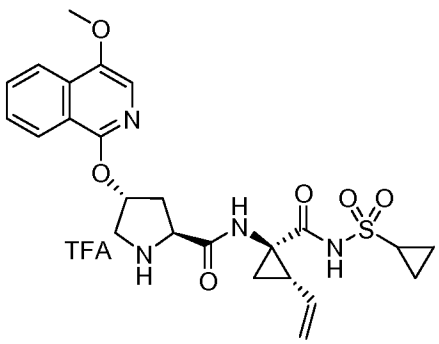
To a solution of (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (2.0 g, 8.6 mmole) and 1-chloro-4-methoxyisoquinoline (2.0 g, 10.3 mmole) in DMSO (15 mL) was added *t*-BuOK (1 M solution in THF, 25.9 mL) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mass was quenched with aqueous citric acid solution and extracted with ethyl acetate (50 mL x 3). The combined organics were washed with water, brine solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (55% ethyl acetate in pet-ether) to get 2.4 g (71.4%) of *(2S,4R)-1-(tert-butoxycarbonyl)-4-((4-methoxyisoquinolin-1-yl)oxy)pyrrolidine-2-carboxylic acid* as gummy liquid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.13-8.12 (m, 2 H), 7.76-7.72 (m, 1 H), 7.60-7.64 (m, 1 H), 7.53 (s, 1 H), 5.70 (s*b*, 1 H), 4.50-4.52 (m, 1 H), 4.08 (s, 3 H), 3.80-3.90 (m, 2 H), 2.71-2.68 (m, 1 H), 2.46-2.40 (m, 1 H), 1.48 (s, 9H); MS: MS *m/z* 389.8 (M^++1).

Step 2: Preperation of *(2S,4R)-tert-butyl 2-(((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)-4-((4-methoxyisoquinolin-1-yl)oxy)pyrrolidine-1-carboxylate:*



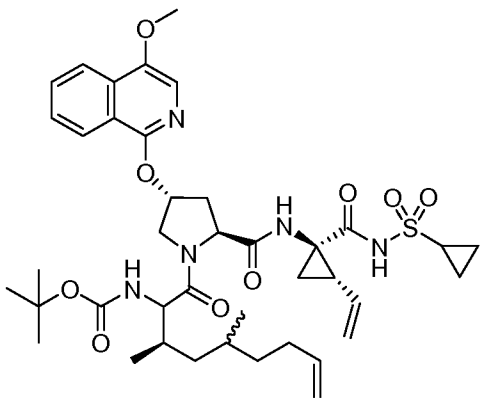
To a solution of *(2S,4R)-1-(tert-butoxycarbonyl)-4-((4-methoxyisoquinolin-1-yl)oxy)pyrrolidine-2-carboxylic acid* (1.1 g, 2.8 mmole) in dichloromethane (15 mL) was added HATU (1.07 g, 2.8 mmole) followed by DIPEA (2.4 mL, 14.1 mmole) at room temperature. The reaction mass was stirred at the same temperature for 10 min. *(1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride* (prepared according to the procedure described in WO 03/099274) was added to the reaction mass and stirred at room temperature for 30 min. The reaction mass was diluted with dichloromethane and washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude compound. The crude compound was purified by silica gel chromatography (70% ethyl acetate in pet ether) to get 1.3 g (76.4%) of *(2S,4R)-tert-butyl 2-(((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)-4-((4-methoxyisoquinolin-1-yl)oxy)pyrrolidine-1-carboxylate* as a white solid. MS: MS *m/z* 601.2 (M^++1).

Step 3: Preperation of TFA salt of *(2S,4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((4-methoxyisoquinolin-1-yl)oxy)pyrrolidine-2-carboxamide*



To a solution of *(2S,4R)-tert-butyl 2-(((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)-4-((4-methoxyisoquinolin-1-yl)oxy)pyrrolidine-1-carboxylate* (1.3 g, 2.1 mmole) in DCM was added trifluoroacetic acid (TFA, 5 mL) at room temperature. The reaction mass was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure to get crude compound *(2S,4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((4-methoxyisoquinolin-1-yl)oxy)pyrrolidine-2-carboxamide* (1.05 g, 97.2%) as a TFA salt. The crude compound was taken to the next step without further purification. MS: MS *m/z* 501.3 (M^++1).

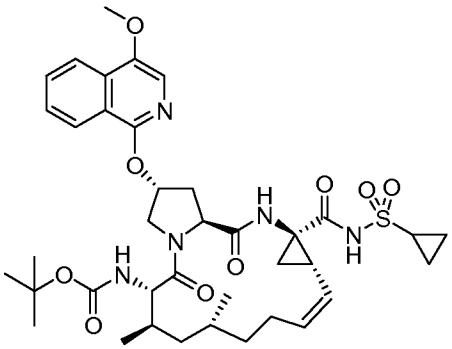
Step 4: Preperation of *tert-butyl ((3R)-1-((2S,4R)-2-(((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)-4-((4-methoxyisoquinolin-1-yl)oxy)pyrrolidin-1-yl)-3,5-dimethyl-1-oxonon-8-en-2-yl)carbamate*



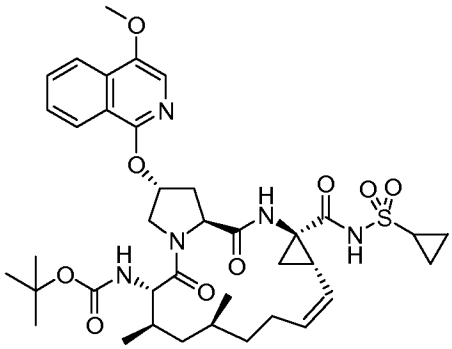
To a solution of *(2S,4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((4-methoxyisoquinolin-1-yl)oxy)pyrrolidine-2-carboxamide* (595 mg, 1.9 mmol) in dichloromethane (15 mL) was added HATU (755 mg, 1.9 mmol) followed by DIPEA (1.7 mL, 9.9 mmole) at room temperature. The reaction mass was stirred at the same temperature for 10 min. *(3R)-2-(tert-butoxycarbonylamino)-3,5-dimethylnon-8-enoic acid* (1.0 g, 1.9 mmole) was added to the reaction mass and the solution was stirred at room temperature for 30 min. The reaction mass was diluted with dichloromethane and washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the

crude compound. The crude compound was purified by silica gel chromatography (70% ethyl acetate in pet ether) to get desired product *tert-butyl ((3R)-1-((2S,4R)-2-(((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)-4-((4-methoxyisoquinolin-1-yl)oxy)pyrrolidin-1-yl)-3,5-dimethyl-1-oxonon-8-en-2-yl)carbamate* as a pale yellow solid. MS: MS *m/z* 782.1 (M^++1).

Step 5: Preperation of Compound 1 & Compound 2



Compound 1



Compound 2

To a degassed solution of *tert-butyl ((3R)-1-((2S,4R)-2-(((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)-4-((4-methoxyisoquinolin-1-yl)oxy)pyrrolidin-1-yl)-3,5-dimethyl-1-oxonon-8-en-2-yl)carbamate* (240 mg, 0.3 mmole) in dichloroethane (100 mL) was added (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine) ruthenium (Grubbs second generation catalyst, 24 mg, 10% w/w) at room temperature under nitrogen atmosphere. The reaction mass was heated at 95 °C overnight. The solvent was evaporated under reduced pressure to afford the desired compound as a diastereomeric mixture.

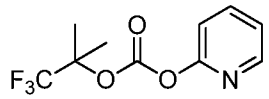
The diastereomers were separated by SFC purification to afford Compound 1 (18 mg, 8%) as a white solid and Compound 2 (8 mg, 3%) as a white solid.

Compound 1: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.18-8.16 (d, *J*= 8.4 Hz, 1 H), 8.11-8.09 (d, *J*= 8.4 Hz, 1 H), 7.74-7.70 (t, *J*= 8 Hz, 1 H), 7.56-7.53(m, 2 H), 5.83 (s*b*, 1 H), 5.63-5.57 (m, 1 H), 5.09-5.01 (m, 1 H), 4.71-4.69 (m, 1 H), 4.62-4.52 (m, 1 H), 4.05-4.04 (m, 4 H), 3.93-3.87 (m, 1 H), 2.92 (m, 1 H), 2.74-2.71 (m, 2 H), 2.43-2.39 (m, 2 H), 2.05-1.98 (m, 1 H), 1.84-1.75 (m, 3 H), 1.59-1.41 (m, 3 H), 1.33-1.23 (m, 4 H), 1.13-1.06 (m, 10 H), 1.03-0.97 (m, 6 H), 0.90-0.83 (m, 1 H); MS: MS *m/z* 755.2 (M^++1).

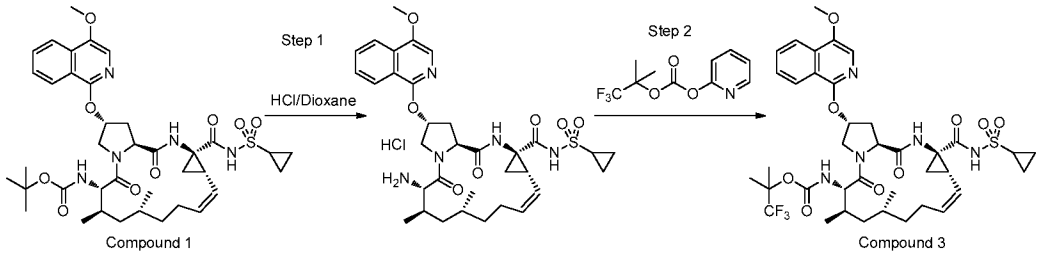
Compound 2: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.18-8.16 (d, *J*= 8.4 Hz, 1 H), 8.11-8.09 (d, *J*= 8.4 Hz, 1 H), 7.74-7.71 (t, *J*= 7.2 Hz, 1 H), 7.59-7.55 (m, 2 H), 5.83 (s*b*, 1 H), 5.63-5.67 (m, 1 H), 5.21-5.19 (m, 1 H), 4.67-4.48 (m, 2 H), 4.02-4.18 (m, 2 H), 4.01 (s, 3 H), 3.08-3.03 (m, 1 H), 2.89-2.88 (m, 1 H), 2.73-2.68 (m, 1 H), 2.50-2.34 (m, 4 H), 2.05-1.95 (m, 2 H), 1.76-1.65 (m, 2 H), 1.47-1.36 (m, 5 H), 1.33-1.24 (m, 6 H), 1.20-1.08 (m, 7 H), 1.03-0.97 (m, 4 H), 0.97-0.92 (m, 1 H); MS: MS *m/z* 806.2 (M^+-1). MS: MS *m/z* 755.3 (M^++1).

Preparation of pyridin-2-yl (1,1,1-trifluoro-2-methylpropan-2-yl) carbonate

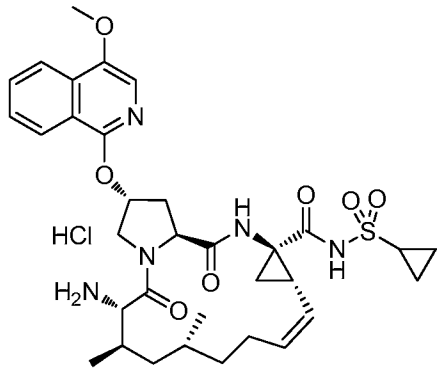


To a slurry of NaH (1.03 g, 25.8 mmol) in THF (70 mL) was added 1,1,1-trifluoro-2-methylpropan-2-ol (3 g, 23.42 mmol). The reaction was stirred at 0 °C for 20 min. A solution of dipyridin-2-yl carbonate (5.06 g, 23.42 mmol) in THF (30 mL) was then added to the mixture. The resulting solution was stirred at room temperature overnight. The residue was filtered washing with EtOAc (2x20 mL). The filtrated was transferred to a separatory funnel and was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting white solid, pyridin-2-yl (1,1,1-trifluoro-2-methylpropan-2-yl) carbonate (1.24 g, 21%), was used in subsequent steps without additional purification..

Scheme:

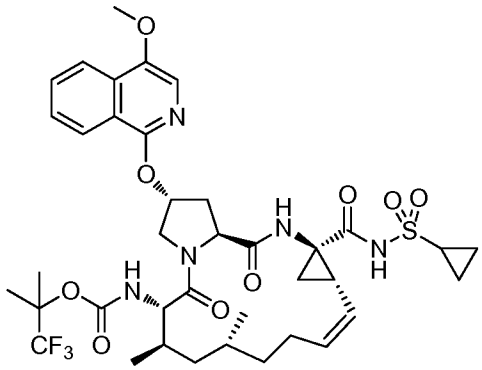


Step 1: Preperation of (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(cyclopropylsulfonyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride



To a solution of HCl in Dioxane was added Compound 1 (300 mg, 0.39 mmol) and the solution was stirred at room temperature for 30 min. The solvent was concentrated under reduced pressure to afford (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(cyclopropylsulfonyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride (250 mg, 96%). The material was triturated with diethyl ether and used in step 2 without further purification. MS: MS *m/z* 655.2 (M^++1).

Step 2: Preperation of Compound 3

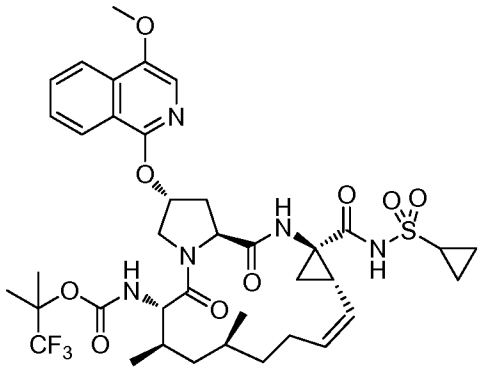


Compound 3

To a solution of (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(cyclopropylsulfonyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride (250 mg, 0.36 mmol) in DCM (4 mL) was added DIPEA (0.3 mL, 1.8 mmole) followed by pyridin-2-yl (1,1,1-trifluoro-2-methylpropan-2-yl) carbonate (180 mg, 0.72 mmole) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The reaction mass was diluted with DCM and washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by HPLC to afford compound 3 (51 mg, 17%) as a white solid.

Compound 3: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17-8.15 (d, *J*= 8.0 Hz, 1 H), 8.13-8.11 (d, *J*= 8.0 Hz, 1 H), 7.75-7.71 (dt, *J*= 6.8 & 1.2 Hz, 1 H), 7.58-7.54 (m, 2 H), 5.82 (m, 1 H), 5.62-5.59 (m, 1 H), 5.08 (m, 1 H), 4.76-4.73 (m, 1 H), 4.66-4.56 (m, 1 H), 4.02 (s, 3 H), 3.99-3.98 (m, 1 H), 3.84-3.81 (m, 1 H), 2.94-2.91 (m, 2 H), 2.47-2.40 (m, 2 H), 2.97-2.75 (m, 4 H), 1.60-1.57 (m, 1 H), 1.50-1.48 (m, 2 H), 1.34-1.22 (m, 6 H), 1.10-0.96 (m, 12 H), 0.85-0.82 (m, 1 H); ^{19}F NMR: δ ppm -85.11 (3 F); MS: MS *m/z* 806.2 (M^+-1).

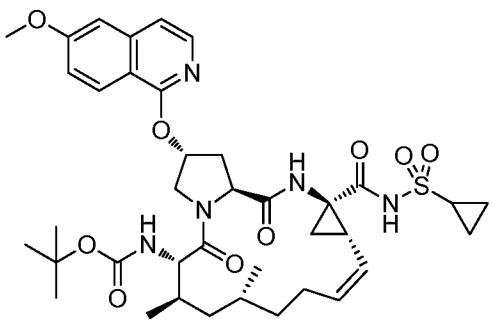
Preparation of Compound 4



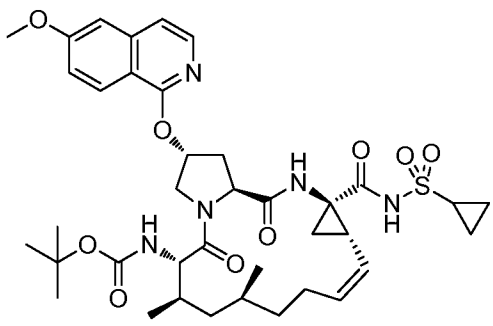
Compound 4

Compound 4 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 808.1 (M^++1).

Preparation of Compounds 5 and 6



Compound 5



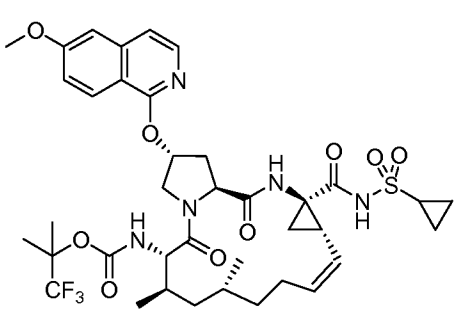
Compound 6

Compounds 5 and 6 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1. Compound 5: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-

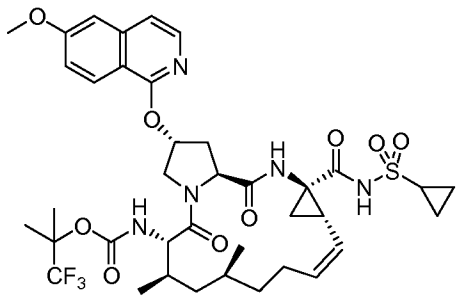
5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.13-8.11 (d, *J*= 8.8 Hz, 1 H), 7.92-7.91 (d, *J*= 6.0 Hz, 1 H), 7.27-7.26 (d, *J*= 6.0 Hz, 1 H), 7.20-7.21 (d, *J*= 2.0 Hz, 1 H), 7.13-7.11 (dd, *J* = 8.8 Hz, 1 H), 5.90 (m, 1 H), 5.75-5.73 (m, 1 H), 5.10-5.05 (m, 1 H), 4.70-4.65 (m, 1 H), 4.51-4.48 (m, 1 H), 4.18-4.17 (m, 1 H), 4.12-4.07 (m, 1 H), 3.94 (s, 3 H), 2.96-2.89 (m, 1 H), 2.74-2.65- (m, 2 H), 2.49-2-42 (m, 2 H), 1.99-1.96 (m, 2 H), 1.74-1.71 (m, 1 H), 1.63-1.62 (m, 2 H), 1.46-1.43 (m, 2 H), 1.25 (m, 11 H), 1.12-1.10 (m, 8 H), 0.94-0.93 (m, 3 H); MS: MS *m/z* 755.2 (M^++1).

Compound 6: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.12-8.10 (d, *J*= 8.8 Hz, 1 H), 7.92-7.90 (d, *J*= 6.0 Hz, 1 H), 7.26-7.25 (d, *J*= 6.0 Hz, 1 H), 7.19-7.20 (d, *J*= 2.4 Hz, 1 H), 7.10-7.07 (dd, *J* = 9.2 and 2.4 Hz, 1 H), 6.67-6.65 (d*b*, 1 H), 5.87-5.89 (m, 1 H), 5.64-5.58 (m, 1 H), 5.07-5.02 (m, 1 H), 4.73-4.70 (m, 1 H), 4.62-4.58 (m, 1 H), 4.04-4.01 (m, 1 H), 3.93 (s, 3 H), 3.90-2.85 (m, 1 H), 2.95-2.91 (m, 1 H), 2.76-2-71 (m, 2 H), 2.45-1.40 (m, 2 H), 1.99-1.95 (m, 1 H), 1.83-1.75 (m, 3 H), 1.60-1.33 (m, 3 H), 1.32-1.24 (m, 2 H), 1.13 (s, 9 H), 1.24-1.08 (m, 3 H), 1.07-0.98 (m, 6 H), 0.86-0.80 (m, 1 H); MS: MS *m/z* 755.2 (M^++1).

Preparation of Compounds 7 and 8



Compound 7



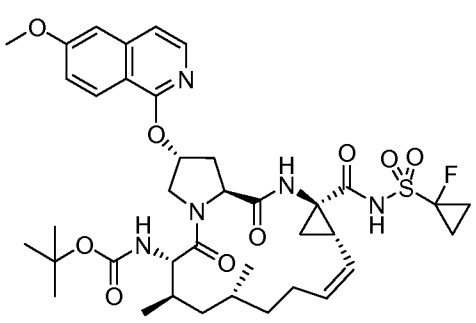
Compound 8

Compounds 7 and 8 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

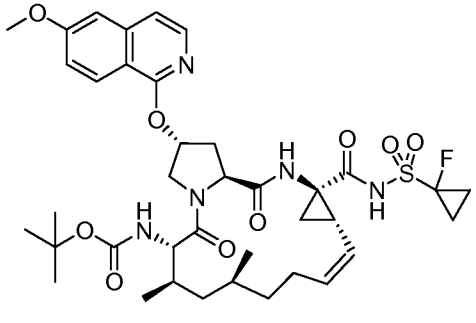
Compound 7: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.11-8.09 (d, *J*= 9.2 Hz, 1 H), 7.93-7.92 (d, *J*= 6.0 Hz, 1 H), 7.28-7.26 (d, *J*= 5.6 Hz, 1 H), 7.21-7.20 (d, *J*= 2.4 Hz, 1 H), 7.12-7.10 (dd, *J*= 9.2 and 2.4 Hz, 1 H), 5.87 (m, 1 H), 5.63-5.62 (m, 1 H), 5.10-5.05 (m, 1 H), 4.75-4.72 (m, 1 H), 4.67-4.62 (m, 1 H), 4.03-3.99 (m, 1 H), 3.94 (s, 3 H), 2.84-2.82 (m, 1 H), 2.96-2.92- (m, 1 H), 2.77-2-71 (m, 2 H), 2.47-1.40 (m, 2 H), 1.98-1.76 (m, 4 H), 1.61-1.51 (m, 1 H), 1.49-1.38 (m, 2 H), 1.35-1.31 (m, 5 H), 1.25-1.22 (m, 1 H), 1.14-1.0 (m, 12 H), 0.98-0.83 (m, 1 H); ^{19}F NMR: -76.94 (3 F), -193.32 (1 F); MS: MS *m/z* 807.1 (M^+-1).

Compound 8: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 807.3 (M^+-1).

Preparation of Compounds 9 and 10



Compound 9



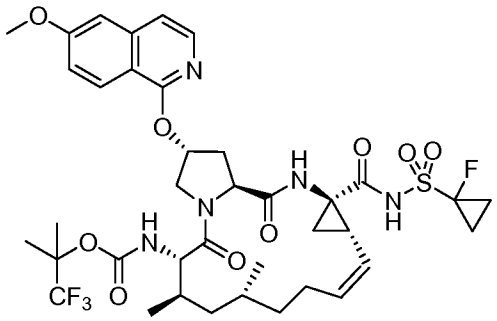
Compound 10

Compounds 9 and 10 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 9: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-fluorocyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.027 (s*b*, 1 H), 8.13-8.11 (d, *J*= 8.8 Hz, 1 H), 7.93-7.91 (d, *J*= 6.0 Hz, 1 H), 7.28-7.27 (d, *J*= 5.6 Hz, 1 H), 7.21-7.20 (d, *J*= 2.4 Hz, 1 H), 7.12-7.09 (dd, J = 9.2 and 2.4 Hz, 1 H), 5.89 (m, 1 H), 5.65-5.58 (m, 1 H), 5.02-4.97 (m, 1 H), 4.74-4.71 (m, 1 H), 4.64-4.60 (m, 1 H), 4.07-4.03 (m, 1 H), 3.94 (s, 3 H), 3.89-3.87 (m, 1 H), 2.78-2.73 (m, 2 H), 2.48-2.38- (m, 2 H), 2.02-1.96 (m, 1 H), 1.88-1.73 (m, 4 H), 1.69-1.59 (m, 2 H), 1.58-1.56 (m, 5 H), 1.29-1.23 (m, 1 H), 1.17 (s, 9 H), 1.03-0.99 (m, 6 H), 0.87-0.81 (m, 1 H); ^{19}F NMR: δ ppm -193.21 (1 F); MS: MS *m/z* 770.2 (M^+-1).

Compound 10: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-fluorocyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.13-8.11 (d, *J*= 9.2 Hz, 1 H), 7.92-7.90 (d, *J*= 6.0 Hz, 1 H), 7.26-7.25 (dt, *J*= 6 Hz, 1 H), 7.20-7.19 (d, *J*= 2 Hz, 2 H), 7.12- 1.10 (d, *J*= 8 Hz, 1 H), 5.89 (m, 1 H), 5.72-5.70 (m, 1 H), 5.04 (m, 1 H), 4.69-4.66 (m, 1 H), 4.51-4.48 (m, 1 H), 4.18-4.09 (m, 2 H), 3.94 (s, 3 H), 2.78-2.63 (m, 2 H), 2.49-2.44- (m, 2 H), 2.0-1-95 (m, 2 H), 1.75-1.64 (m, 4 H), 1.49-1.40 (m, 4 H), 1.33-1.17 (m, 11 H), 1.25-1.11 (m, 5 H), 0.98-0.91 (d, *J*= 7 Hz, 3H); ^{19}F NMR: δ ppm 193.32 (1 F); MS: MS *m/z* 773.2 (M^++1).

Preparation of Compound 11

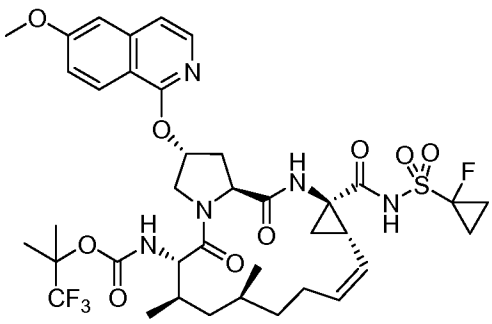


Compound 11

Compound 11 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 11: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-fluorocyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.11-8.08 (d, *J*= 9.2 Hz, 1 H), 7.93-7.91 (d, *J*= 6.0 Hz, 1 H), 7.27-7.26 (dt, *J*= 6 Hz, 1 H), 7.21-7.20 (d, *J*= 2.4 Hz, 1 H), 7.12-.7.09 (dd, *J*= 9.2 and 2.4 Hz, 1 H), 5.87 (m, 1 H), 5.61-5.59 (m, 1 H), 4.94 (m, 1 H), 4.74-4.71 (m, 1 H), 4.67-4.62 (m, 1 H), 4.03-4.0 (m, 1 H), 3.94 (s, 3 H), 3.86-2.81 (m, 1 H), 2.77-2.72- (m, 3 H), 2.48-2-36 (m, 2 H), 1.99-1.80 (m, 2 H), 1.79-1.72 (m, 2 H), 1.66-1.58 (m, 4 H), 1.49 (sb, 3 H), 1.46-1.22 (m, 2 H), 1.02-0.97 (m, 9 H), 0.86-0.79 (m, 1 H); ^{19}F NMR: δ ppm -85.08 (1 F), -193.20 (1 F); MS: MS *m/z* 826.2 (M^++1).

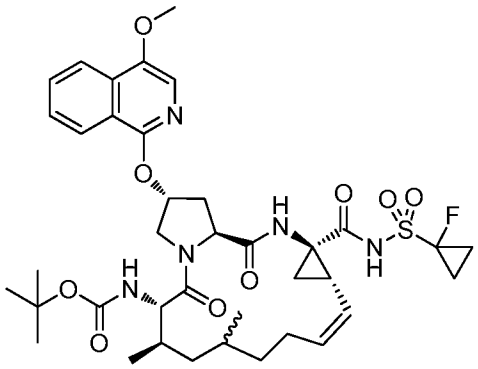
Preparation of Compound 12



Compound 12

Compound 12 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-fluorocyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 826.2 (M^++1).

Preparation of Compound 13

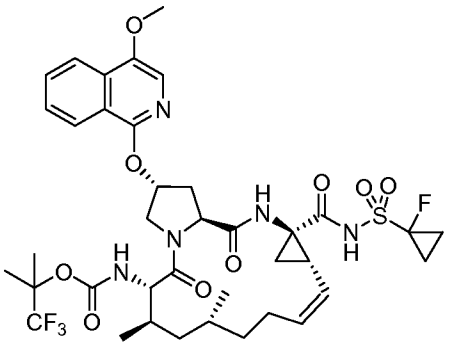


Compound 13

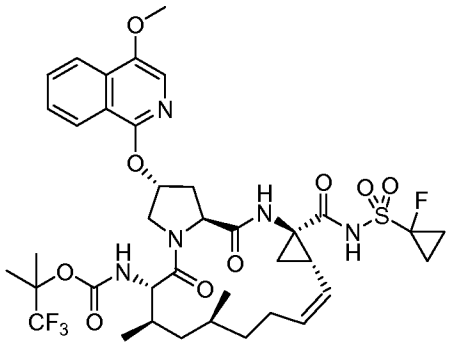
Compound 13 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 13: tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-(((1-fluorocyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.20-8.12 (m, 2 H), 7.79-7.70 (m, 1 H), 7.64-7.52 (m, 2 H), 5.90-5.80 (m, 1 H), 5.65-5.55 (m, 1 H), 5.10-4.95 (m, 1 H), 4.75-4.55 (m, 1 H), 4.39-4.16 (m, 1 H), 4.05 (s, 3 H), 4.01-3.95 (m, 1 H), 2.82-2.70 (m, 2 H), 2.49-2-37 (m, 2 H), 2.10-1.95 (m, 2 H), 1.87-1.70 (m, 4 H), 1.67-1.55 (m, 2 H), 1.50-1.40 (m, 5 H), 1.37-1.25 (m, 1 H), 1.20 (s, 9 H), 1.10-0.90 (m, 6 H), 0.85-0.70 (m, 1H); MS: MS *m/z* 773 (M^++1).

Preparation of Compounds 14 and 15



Compound 14



Compound 15

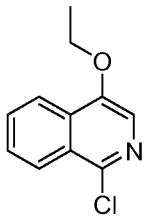
Compounds 14 and 15were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 14: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-fluorocyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.04 (s*b*, 1 H), 8.18-8.15 (d*b*, *J*= 8.4 Hz, 1 H), 8.13-8.11 (d*b*, *J*= 8.4 Hz, 1 H), 7.76-7.71 (dt, *J*= 6.8 and 1.2 Hz, 1 H), 7.58-7.54 (m, 2 H), 5.85 (s*b*, 1 H), 5.63-5.59 (m, 1 H), 5.01-5.96 (m, 1 H), 4.77-4.74 (m, 1 H), 4.68-4.63 (m, 1 H), 4.03 (s, 3 H), 4.01-3.99 (m, 1 H), 3.84-3.81 (m, 1 H), 2.77-2.73 (m, 2 H), 2.47-2-40 (m, 2 H), 1.98-1.80 (m, 2 H), 1.79-1.73 (m, 3 H), 1.67-1.57 (m, 3 H), 1.54-1.43 (m, 4 H), 1.34 (s*b*, 3 H), 1.30-1.22 (m, 2 H), 1.02-0.96 (m, 9 H), 0.86-0.80 (m, 1 H); ^{19}F NMR: δ ppm -85.11 (3 F), -193.22 (1 F); MS: MS *m/z* 827.3 (M^++1).

Compound 15: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-fluorocyclopropyl)sulfonyl)carbamoyl)-2-((4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.19-8.17 (d, *J*= 8.0 Hz, 1 H), 8.13-8.11 (d, *J*= 8.4 Hz, 1 H), 7.76-7.72 (dt, *J*= 7.2 and

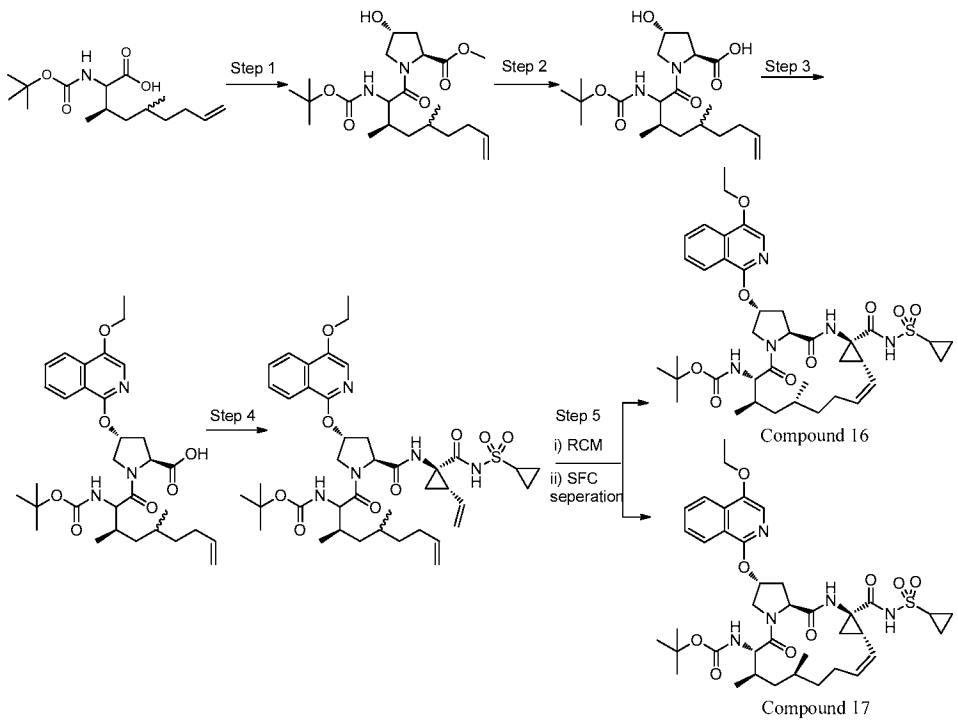
1.2 Hz, 1 H), 7.59-7.55 (m, 2 H), 5.85 (s*b*, 1 H), 5.33-5.70 (m, 1 H), 5.05-5.0 (m, 1 H), 4.73-4.69 (m, 1 H), 4.57-4.54 (m, 1 H), 4.11-4.04 (m, 2 H), 4.02 (s, 3 H), 2.76-2.60 (m, 3 H), 2.58-2.42 (m, 2 H), 2.01-1.98 (m, 2 H), 1.78-1-61 (m, 5 H), 1.60-1.41 (m, 7 H), 1.30-1.21 (m, 4 H), 1.19-1.18 (m, 3 H), 1.15-1.10 (m, 2 H), 0-.94-0.93 (m, 3 H); ^{19}F NMR: δ ppm -85.05 (3 F), -193.33 (1 F); MS: MS *m/z* 825.2 (M^+-1).

Preparation of 1-chloro-4-ethoxyisoquinoline

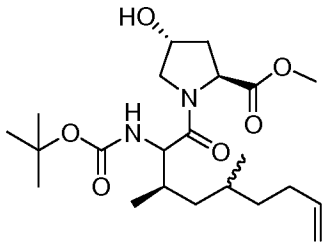


To a solution of 1-chloroisoquinolin-4-ol (1.0 g, 5.5 mmole) in acetonitrile (10 mL) was added K_2CO_3 (2.3 g, 16.7 mmole) followed by ethyl iodide (0.87 mL, 11.0 mmole) at room temperature. The reaction mixture was stirred at room temperature for overnight. Solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced. The resulting residue was purified by silica gel chromatography to afford 1-chloro-4-ethoxyisoquinoline (700 mg, 62%) as an off-white solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.26-8.24 (m, 2 H), 7.79 (s, 1 H), 7.76-7.26 (m, 2 H), 4.29-4.24 (q, *J*= 6.8 Hz, 2 H), 1.58-1.1.54 (t, J= 6.8 Hz, 3 H); MS: MS *m/z* 207.7 (M^++1).

Scheme



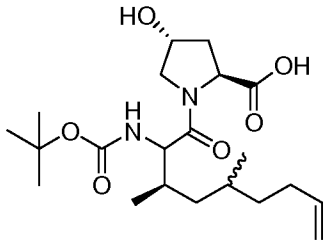
Step 1: Preparation of *(2S,4R)-methyl 1-((3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylate:*



To a solution of (3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoic acid (2 g, 6.6 mmole), synthesized using Scheme 1, in dichloromethane (20 mL) was added DIPEA (11.5 mL, 33.0 mmole), HATU (2.7 g, 7.2 mmole) followed by (2S,4R)-methyl 4-hydroxypyrrolidine-2-carboxylate (1.3 g, 7.2 mmole) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The reaction mass was diluted with DCM and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude *(2S,4R)-methyl 1-((3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylate*. The crude product was taken to the next step

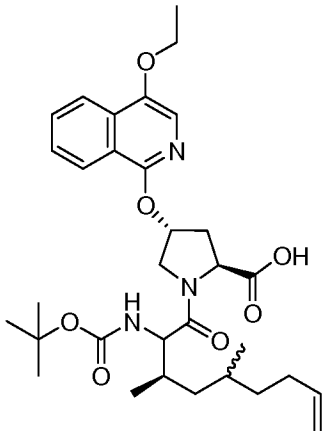
without further purification (2.2 g, 80%). MS: MS *m/z* 427.2 (M^++1).

Step 2: Preparation of *(2S,4R)-1-((3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylic acid:*



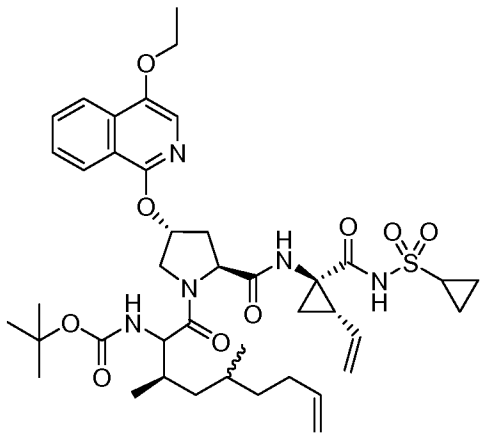
To a solution of *(2S,4R)-methyl 1-((3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylate* (2.2 g, 5.1 mmole) in THF/water (20 mL, 1: 1) was added LiOH (650 mg, 15 mmole) followed by 5 mL of methanol at room temperature. The reaction mass was stirred at room temperature for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with water and acidified with aqueous 1.5 N HCl solution. The aqueous solution was extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get desired product (2S,4R)-1-((3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylic acid (1.8 g, 85%) as white solid. MS: MS *m/z* 411.2 (M^+-1).

Step 3: Preparation of *(2S,4R)-1-((3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-((4-ethoxyisoquinolin-1-yl)oxy)pyrrolidine-2-carboxylic acid:*



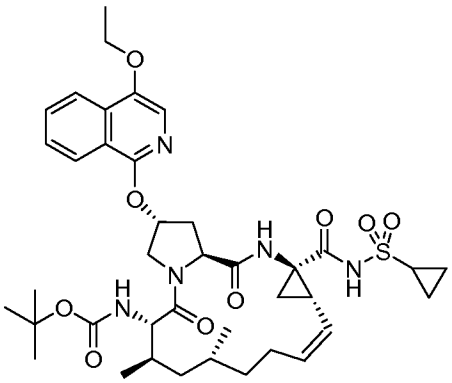
To a solution of *(2S,4R)-1-((3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylic acid* (700 mg, 1.6 mmole) in DMSO was added 1-chloro-4-ethoxyisoquinoline (420 mg, 2.0 mmole), prepared above, followed by *t*-BuOK (1M sol. in THF, 8 mL, 8 mmole) at room temperature under nitrogen atmosphere. The reaction mass was stirred at room temperature for 4 h. The reaction mass was quenched with aqueous citric acid solution and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude compound. The crude compound was purified by combiflash to get desired product (2S,4R)-1-((3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-((4-ethoxyisoquinolin-1-yl)oxy)pyrrolidine-2-carboxylic acid (600 mg, 64%) as off-white solid. MS: MS *m/z* 585.1 (M^++1).

Step 4: Preparation of *tert-butyl ((3R)-1-((2S,4R)-2-(((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)-4-((4-ethoxyisoquinolin-1-yl)oxy)pyrrolidin-1-yl)-3,5-dimethyl-1-oxonon-8-en-2-yl)carbamate:*

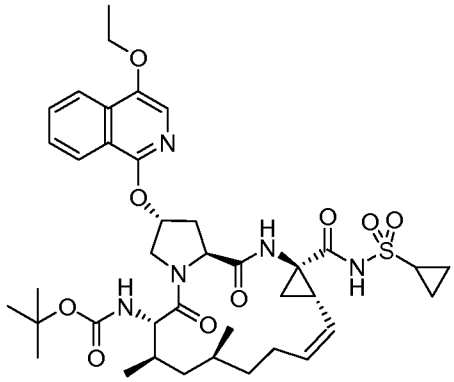


To a solution of (2S,4R)-1-((3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-((4-ethoxyisoquinolin-1-yl)oxy)pyrrolidine-2-carboxylic acid (600 mg, 1.0 mmole) in dichloromethane (10 mL) was added DIPEA (0.87 mL, 5 mmole), HATU (380 mg, 1.0 mmole) followed by (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride (prepared according to the procedure described in WO 03/099274) (457 mg, 1.1 mmole) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The reaction mass was diluted with DCM and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired product *tert-butyl ((3R)-1-((2S,4R)-2-(((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)-4-((4-ethoxyisoquinolin-1-yl)oxy)pyrrolidin-1-yl)-3,5-dimethyl-1-oxonon-8-en-2-yl)carbamate* (500 mg, 61%) as off-white solid. MS: MS *m/z* 797.2 (M^++1).

Step 5: Preparation of Compounds 16 and 17



Compound 16



Compound 17

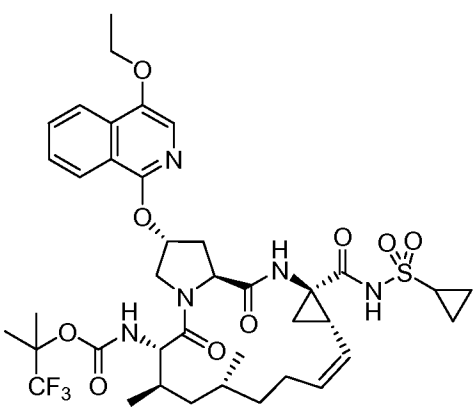
Compounds 16 and 17 were prepared using the intermediates described above and by following the general procedure described for the synthesis of Compound 1 and Compound 2, step 5.

Compound 16: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17-8.15 (d, *J*=8.4 Hz, 1 H), 8.13-8.11 (d, *J*= 8 Hz, 1 H), 7.74-7.70 (t, *J*= 7.2 Hz, 1 H), 7.56-7.52 (m, 2 H), 5.83 (m, 1 H), 5.65.5.59 (m, 1 H), 5.06-5.01 (m, 1 H), 4.73-4.70 (m , 1 H), 4.63-4.56 (m, 2 H), 4.25-4.20 (q, *J*= 6.8 Hz, 2 H), 4.04-4.01 (m, 1 H), 3.90-3.86 (m, 1 H), 2.94-2.92 (m, 1 H), 2.76-2.71 (m, 2 H), 2.44-2.38 (m, 2 H), 1.98-1.95 (m, 1 H), 1.96-1.76 (m, 3 H), 1.60-1.46 (m, 6 H), 1.35-1.30 (m, 3 H), 1.18-1.10 (m, 11 H), 1.09-0.98 (m, 6 H), 0.86-0.80 (m, 1 H); MS: MS *m/z* 769.1 (M^++1).

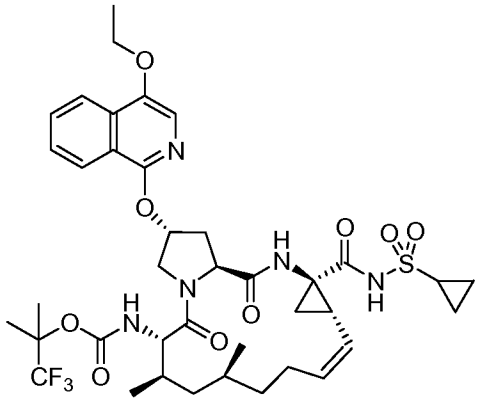
Compound 17: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.19-8.17 (d, *J*= 8 Hz, 1 H), 8.15-8.13 (d, *J*=8.4 Hz, 1 H), 7.75-7.72 (t, *J*= 8 Hz, 1 H), 7.59-7.55 (m, 2 H), 5.85 (m, 1 H), 5.75-5.73 (m, 1 H), 5.08 (m, 1 H), 4.70-4.66 (m , 1 H), 4.52-4.49 (m, 1 H), 4.26-4.21 (q, *J*= 6.8

Hz, 2 H), 4.17-4.16 (m, 1 H), 4.10-4.07 (m, 1 H), 2.96-2.90 (m, 1 H), 2.74-2.65 (m, 2 H), 2.48-2.42 (m, 2 H), 1.99-1.96 (m, 2 H), 1.75-1.71 (m, 1 H), 1.61 (m, 2 H), 1.56-1.52 (t, *J*=6.8 Hz, 3 H), 1.46-1.40 (m, 2 H), 1.31-1.27 (m, 11 H), 1.13-1.0 (m, 8 H), 0.95-0.93 (m, 3 H); MS: MS *m/z* 769.1 (M^++1).

Preparation of Compounds 18 and 19



Compound 18



Compound 19

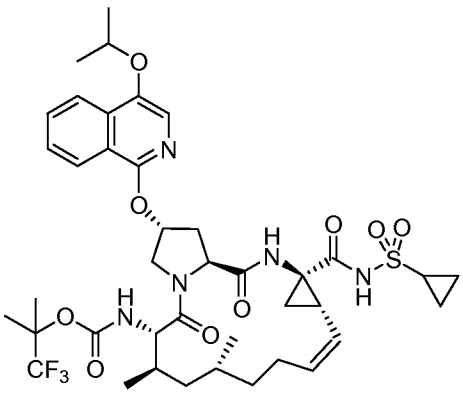
Compounds 18 and 19 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 18: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17-8.13 (m, 2 H), 7.76-7.72 (dt, *J*= 6.8 and 1.2 Hz, 1 H), 7.58-7.54 (m, 2 H), 5.83 (m, 1 H), 5.63.5.62 (m, 1 H), 5.05 (m, 1 H), 4.77-4.74 (m , 1 H), 4.67-4.63 (m, 1 H), 4.27-4.21 (q, *J*= 6.8 Hz, 2 H), 4.02-3.98 (m, 1 H), 3.84-3.82 (m, 1 H), 2.95-2.92 (m, 1 H), 2.75-2.72 (m, 2 H), 2.46-2.40 (m, 2 H), 1.96-1.80 (m, 4 H), 1.61-1.53 (m, 6 H), 1.35-1.31 (m, 5 H), 1.27-1.14 (m, 4 H), 1.09-1.0.98 (m, 9 H), 0.96-0.90 (m, 1 H), ^{19}F NMR: δ ppm -85.11 (3 F); MS: MS *m/z* 822.2 (M^++1).

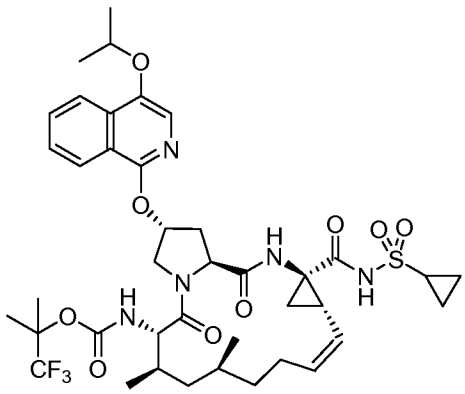
Compound 19: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-

ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.18-8.16 (d, *J*= 8 Hz, 1 H), 8.14-8.12 (d, *J*=8.8 Hz, 1 H), 7.75-7.71 (dt, *J*= 6.8 and 1.2 Hz, 1 H), 7.58-7.55 (m, 2 H), 5.83 (m, 1 H), 5.75-5.73 (m, 1 H), 5.08 (m, 1 H), 4.72-4.65 (m, 1 H), 4.56-4.53 (m, 2 H), 4.26-4.20 (q, *J*= 7.2 Hz, 2 H), 4.12-4.11 (m, 2 H), 2.92-2.90 (m, 1 H), 2.74-2.66 (m, 2 H), 2.49-2.46 (m, 2 H), 2.03-2.01 (m, 2 H), 1.75-1.73 (m, 3 H), 1.65-1.54 (t, *J*=7.2 Hz, 3 H), 1.48-1.38 (m, 5 H), 1.30-1.23 (m, 6 H), 1.14-1.01 (m, 9 H), 0.94-0.87 (m, 1 H); ^{19}F NMR: δ ppm -85.04 (3 F); MS: MS *m/z* 822.2 (M^++1).

Preparation of Compounds 20 and 21



Compound 20



Compound 21

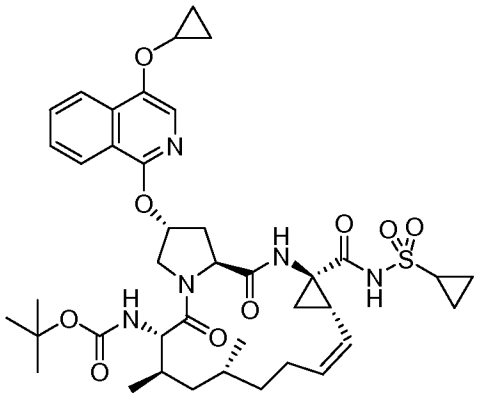
Compounds 20 and 21 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 20: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.0 (s*b*, 1 H), 8.16-8.14 (d, *J*= 8.4, 1 H), 8.12-8.10 (d, *J*= 8.4, 1 H), 7.74-7.70 (dt, *J*= 7.2 and 1.2 Hz, 1 H), 7.61 (s , 1 H), 7.57-7.53 (m, 1 H), 5.82 (m, 1 H), 5.64.5.59 (m, 1 H), 5.06-5.01 (m, 1 H), 4.94-4.90 (m, 1 H), 4.80-4.71 (m, 2 H), 4.69-4.63 (m, 1 H),

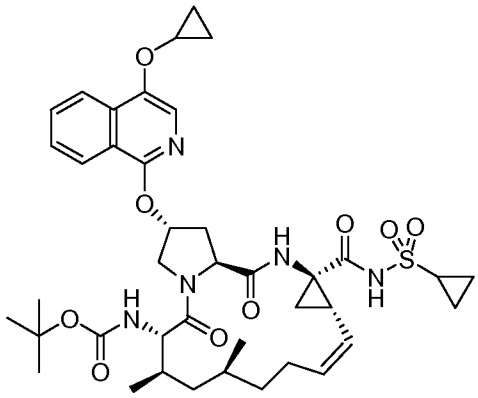
4.02-3.98 (m, 1 H), 3.83-3.81 (m, 1 H), 2.95-2.91 (m, 1 H), 2.77-2.71 (m, 2 H), 2.46-2.40 (m, 2 H), 1.81-1.76 (m, 4 H), 1.60-1.57 (m, 1 H), 1.51-1.44 (m, 8 H), 1.33-1.30 (m, 5 H), 1.16-0.98 (m, 9 H), 0.97 (m, 3 H), 0.91-0.83 (m, 1 H); ^{19}F NMR: δ ppm -85.13 (3 F); MS: MS *m/z* 836.2 (M^++1).

Compound 21: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.03 (s*b*, 1 H), 8.18-8.16 (d, *J*= 8.4, 1 H), 8.12-8.10 (d, *J*= 8.4, 1 H), 7.75-7.70 (dt, *J*= 7.2 and 1.2 Hz, 1 H), 7.60 (s , 1 H), 7.58-7.54 (m, 1 H), 5.84 (m, 1 H), 5.73.5.71 (m, 1 H), 5.10-5.05 (m, 1 H), 4.75-4.70 (m, 2 H), 4.69-4.56 (m, 1 H), 4.10-4.03 (m, 2 H), 2.98-2.90 (m, 1 H), 2.78-2.61 (m, 2 H), 2.50-2.45 (m, 2 H), 2.01-1.99 (m, 2 H), 1.74-1.58 (m, 3 H), 1.49-1.42 (m, 11 H), 1.35-1.21 (m, 4 H), 1.15-1.02 (m, 9 H), 0.95-0.93 (m, 3 H); ^{19}F NMR: δ ppm -85.05 (3 F); MS: MS *m/z* 836.3 (M^++1).

Preparation of Compounds 22 and 23



Compound 22



Compound 23

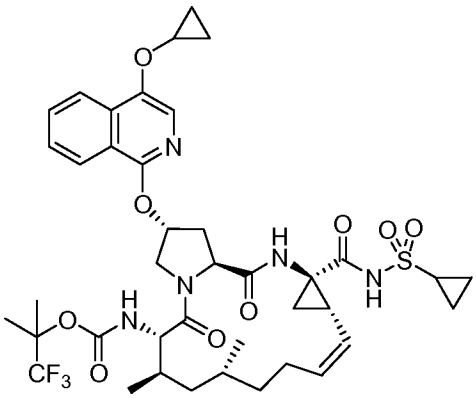
Compounds 22 and 23 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 22: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-cyclopropoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

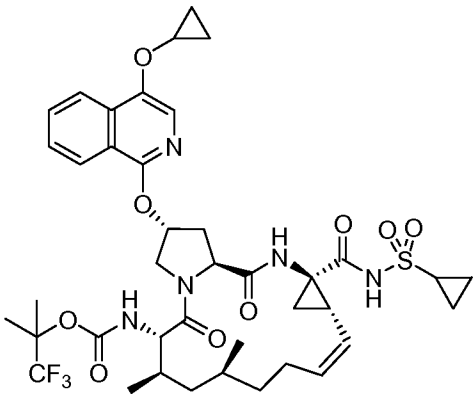
hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17-8.15 (d, *J*= 8.0 Hz, 1 H), 8.02-8.00 (d, *J*= 8.4 Hz, 1 H), 7.87 (s, 1 H), 7.72-7.68 (t, *J*= 7.2 Hz, 1 H), 7.56-7.52 (t, *J*= 8 Hz, 1 H), 6.62-6.60 (db, 1H), 5.84-5 (m, 1 H), 5.65-5.59 (m, 1 H), 5.06-5.01 (m, 1 H), 4.75-4.72 (m, 1 H), 4.64-4.56 (m, 1 H), 4.05-3.97 (m, 2 H), 3.97-3.3.90 (m, 1 H), 2.95-2.91 (m, 1 H), 2.77-2-72 (m, 2 H), 2.43-2.40 (m, 2 H), 2.02-1.98 (m, 1 H), 1.83-1.76 (m, 3 H), 1.60-1.56 (m, 1 H), 1.51-1.48 (m, 2 H), 1.34-1.30 (m, 2 H), 1.25-1.21 (m, 1 H), 1.18-1.06 (m, 10 H), 1.05-0.97 (m, 8 H), 0.91-0.81 (m, 4 H); MS: MS *m/z* 781.2 (M^++1).

Compound 23: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-cyclopropoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 781.2 (M^++1).

Preparation of Compounds 24 and 25



Compound 24



Compound 25

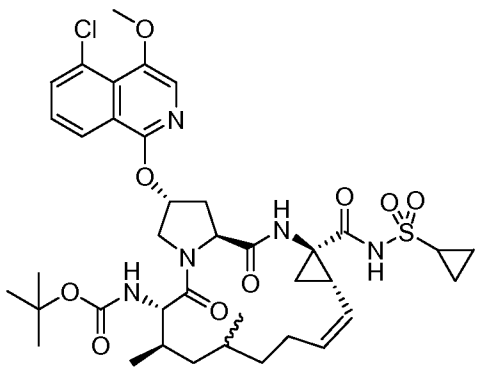
Compounds 24 and 25 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 24: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-cyclopropoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17-8.15 (d, *J*= 8.4 Hz, 1 H), 8.04-8.02 (d, *J*= 8.4 Hz, 1 H), 7.88 (s, 1 H), 7.73-7.69 (dt, *J*= 7.1 and 1.2 Hz, 1 H), 7.57-7.53 (dt, *J*= 8 and 1.2 Hz, 1 H), 7.27-7.25 (d*b*, 1H), 5.84-5.83 (m, 1 H), 5.66-5.59 (m, 1 H), 5.06-5.01 (m, 1 H), 4.78-4.75 (m, 1 H), 4.67-4.63 (m, 1 H), 4.02-3.97 (m, 2 H), 3.85-3.80 (m, 1 H), 2.94-2.91 (m, 1 H), 2.76-2-71 (m, 2 H), 2.44-2.40 (m, 2 H), 1.90-1.81 (m, 4 H), 1.67-1.57 (m, 2 H), 1.52-1.49 (m, 1 H), 1.49-1.37 (m, 4 H), 1.14-1.10 (m, 3 H), 1.08-0.97 (m, 7 H), 0.91-0.80 (m, 8 H); ^{19}F NMR: δ ppm -85.11 (3 F); MS: MS *m/z* 832.2 (M^+-1).

Compound 25: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-cyclopropoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.18-8.16 (d, *J*= 8.0 Hz, 1 H), 8.03-8.01 (d, *J*= 8.4 Hz, 1 H), 7.88 (s, 1 H), 7.73-7.69 (dt, *J*= 7.2 and 1.2 Hz, 1 H), 7.58-7.54 (dt, *J*= 8 and 1.2 Hz, 1 H), 7.21-7.19 (d*b*, 1H), 5.84 (m, 1 H), 5.73-5.71 (m, 1 H), 5.10-5.06 (m, 1 H), 4.72-4.68 (m, 1 H), 4.58-4.55 (m, 1 H), 413-3.98 (m, 3 H), 2.93-2.91 (m, 1 H), 2.73-2-70 (m, 2 H), 2.52-2.45 (m, 2 H), 2.02-1.95 (m, 2 H), 1.72-1.63 (m, 4 H), 1.49-1.43 (m, 4 H), 1.34-1.22 (m, 3 H), 1.12-1.02 (m, 9 H), 0.95-0.83 (m, 8 H); ^{19}F NMR: δ ppm -85.04 (3 F); MS: MS *m/z* 832.3 (M^+-1).

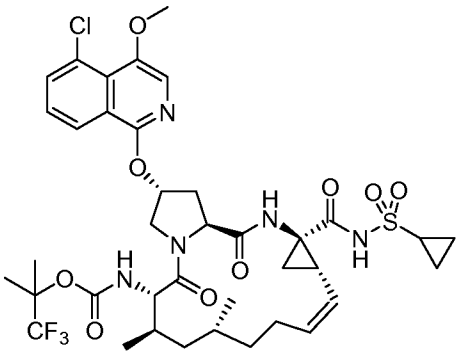
Preparation of Compound 26



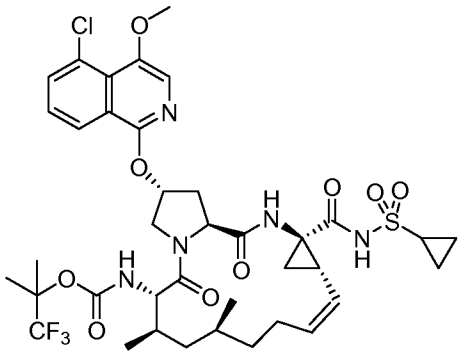
Compound 26

Compound 26 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1. Compound 26: tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-2-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 789.2 (M^++1).

Preparation of Compounds 27 and 28



Compound 27

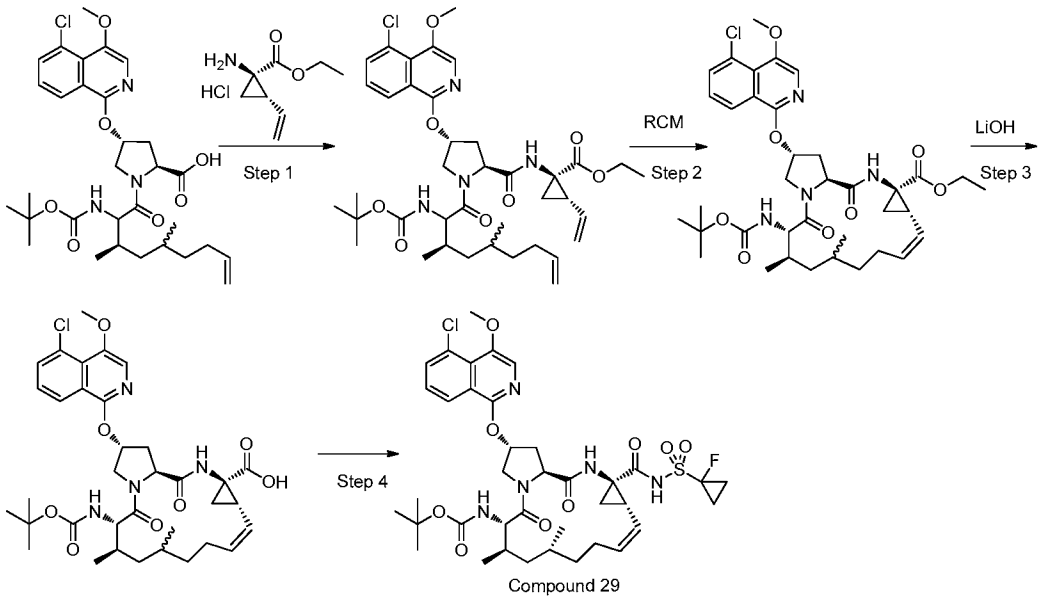


Compound 28

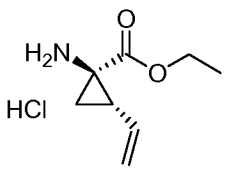
Compounds 27 and 28 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 27: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.0 (s*b*, 1 H), 8.18-8.16 (dd, *J*= 8.0 and 1.2 Hz, 1 H), 7.78-7.76 (dd, J= 7.6 and 1.2 Hz, 1 H), 7.71 (s, 1 H), 7.49-7.45 (t*b*, J= 8.0 Hz, 1 H), 5.83-5.82 (m, 1 H), 5.65.5.59 (m, 1 H), 5.06-5.01 (m, 1 H), 4.78-4.75 (m, 1 H), 4.67-4.65 (m, 1 H), 4.0-3.96 (m, 4 H), 3.79-3.77 (m, 1 H), 2.97-2.91 (m, 1 H), 2.75-2.70 (m, 2 H), 2.46-2.39 (m, 2 H), 2.01-1.92 (m, 1 H), 1.82-1.76 (m, 3 H), 1.60-1.57 (m, 1 H), 1.50-1.49 (m, 2 H), 1.35-1.30 (m, 4 H), 1.26-1.21 (m, 2 H), 1.16-1.07 (m, 3 H), 1.07-0.98 (m, 9 H), 0.85-0.82 (m, 1 H); ^{19}F NMR: δ ppm -85.10 (3 F); MS: MS *m/z* 841.2 (M^+-1).

Compound 28: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.20-8.18 (dd, *J*= 8.4 and 1.2 Hz, 1 H), 7.79-7.76 (dd, *J*= 7.6 and 1.2 Hz, 1 H), 7.70 (s, 1 H), 7.49-7.45 (t*b*, *J*= 8.0 Hz, 1 H), 7.22-7.20 (s*b*, 1 H), 5.84-5.82 (m, 1 H), 5.73.5.71 (m, 1 H), 5.10-5.05 (m, 1 H), 4.72-4.68 (m, 1 H), 4.58-4.55 (m, 1 H), 4.09-4.01 (m, 2 H), 3.96 (s, 3 H), 2.93-2.91 (m, 1 H), 2.75-2.68 (m, 2 H), 2.51-2.45 (m, 2 H), 1.99-1.95 (m, 2 H), 1.74-1.70 (m, 2 H), 1.62-1.59 (m, 2 H), 1.49-1.43 (m, 4 H), 1.35-1.30 (m, 4 H), 1.18-1.05 (m, 9 H), 0.94-0. (m, 3 H); ^{19}F NMR: δ ppm -85.04 (3 F); MS: MS *m/z* 841.2 (M^+-1).

Scheme:

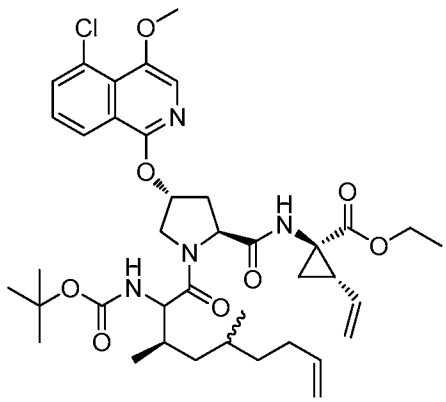


Preparation (1R,2S)-ethyl 1-amino-2-vinylcyclopropanecarboxylate hydrochloride



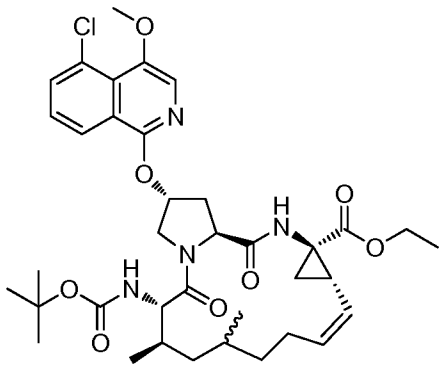
A solution of (1R,2S)-ethyl 1-(tert-butoxycarbonylamino)-2-vinylcyclopropanecarboxylate (prepared according to the procedure described in WO 03/099274, Page No. 53-59) (1.0 g, 4.4 mmol) in ethanolic HCl (10 mL) was stirred at 70 °C for overnight. The solvent was evaporated under reduced pressure and the residue washed with diethyl ether to get crude compound as semi solid. The crude compound was taken to the next step without further purification. MS: MS *m/z* 156 (M^++1).

Step 1: Preparation of *(1R,2S)-ethyl 1-((2S,4R)-1-((3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate:*



A procedure was followed analogous to that described for *tert-butyl ((3R)-1-((2S,4R)-2-(((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)-4-((4-methoxyisoquinolin-1-yl)oxy)pyrrolidin-1-yl)-3,5-dimethyl-1-oxonon-8-en-2-yl)carbamate* to afford (1R,2S)-ethyl 1-((2S,4R)-1-((3R)-2-((tert-butoxycarbonyl)amino)-3,5-dimethylnon-8-enoyl)-4-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate. MS: MS *m/z* 742.3 (M^++1).

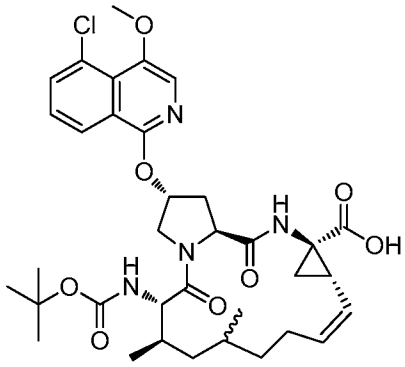
Step 2: Preparation of *(2R,6S,7R,13aS,14aR,16aS,Z)-ethyl 6-((tert-butoxycarbonyl)amino)-2-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate:*



The general procedure as described for Compound 1 and 2 was followed with the modification that the diastereomer products were not separated.

MS: MS *m/z* 714 (M^++1).

Step 3: Preparation of *(2R,6S,7R,13aS,14aR,16aS,Z)-6-((tert-butoxycarbonyl)amino)-2-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylic acid:*

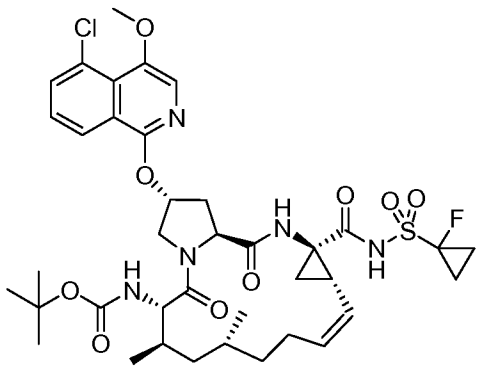


To a solution of (2R,6S,7R,13aS,14aR,16aS,Z)-ethyl 6-((tert-butoxycarbonyl)amino)-2-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-

carboxylate (400 mg, 0.56 mmol) in THF/water (1: 1) was added LiOH (235 mg, 5.61 mmol) followed by 5 mL of methanol at room temperature. The reaction mixture was stirred at room temperature for overnight. The solvent was removed under reduced pressure and the residue was diluted with water and acidified by aqueous 1.5 N HCl solutions. The aqueous solution was extracted with ethyl acetate. The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated to get desired product (2R,6S,7R,13aS,14aR,16aS,Z)-6-((tert-butoxycarbonyl)amino)-2-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylic acid as diastereomeric mixture (310 mg, 81%).

MS: MS *m/z* 686.3 (M^++1).

Step 4: Preparation of Compound 29:

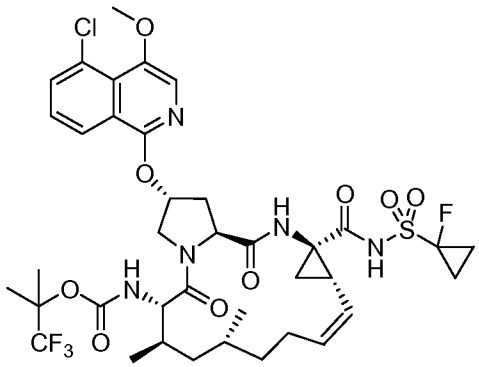


Compound 29

To a solution of (2R,6S,7R,13aS,14aR,16aS,Z)-6-((tert-butoxycarbonyl)amino)-2-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylic acid (300 mg, 0.43 mmol) in DMF (20 mL) was added 1,1′-carbonyldiimidazole (CDI, 92 mg, 0.57 mmol) at room temperature. The reaction mass was heated at 50 °C for 2 h. To this hot solution was added 1-fluorocyclopropane-1-sulfonamide TFA (166 mg, 0.65 mmol) followed by DBU (135 mg, 0.87 mmol). The resulting solution was stirred at 50 °C for overnight. The

reaction mass was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get desired product as diastereomeric mixture. The diastereomeric mixture was separated by HPLC to get desired product *Compound 29* (110 mg, 33%). tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)-14a-(((1-fluorocyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate MS: MS *m/z* 808.2 (M^++1).

Preparation of Compound 30



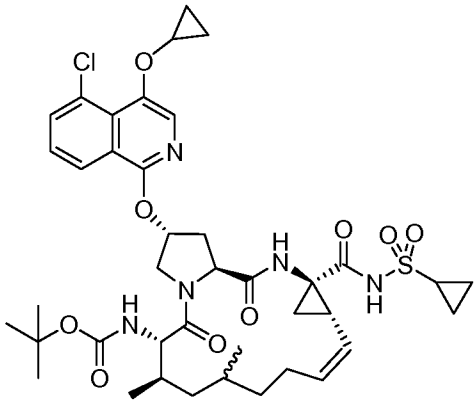
Compound 30

Compound 30 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 30: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)-14a-(((1-fluorocyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.18-8.18 (dd, *J*= 8.2 Hz & 1.2, 1 H), 7.78-7.76 (dd, *J*= 7.6 & 1.2 Hz, 1 H), 716 (s*b*, 1 H), 7.49-7.45 (t, *J* = 8 Hz, 1 H), 7.27-7.25 (d*b*, 1 H), 5.83 (m, 1 H), 5.60-5.58 (m, 1 H), 4.77-4.74 (m, 1 H), 4.64-4.56 (m, 1 H), 4.01-4.0 (m, 1 H), 4.98 (s, 3 H), 3.81-3.77 (m, 1 H), 2.77-2.72 (m, 2 H), 2.45-2-39 (m, 2 H), 1.99-1.59 (m, 7 H), 1.55-1.39 (m, 5

H), 1.38-1.20 (m, 6 H), 1.04-0.91 (m, 7 H), 0.87-0.76 (m, 1 H); ^{19}F NMR: δ ppm -85.10 (3 F), 193.21 (1 F); MS: MS *m/z* 860.9 (M^++1).

Preparation of Compound 31

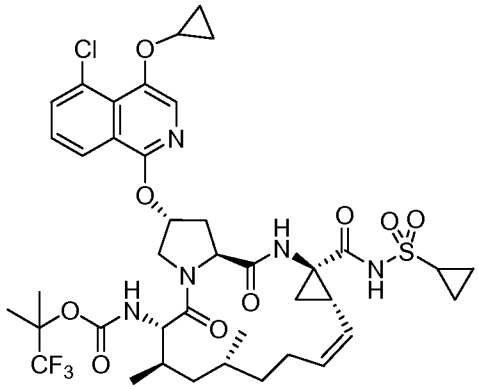


Compound 31

Compound 31 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 31: tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-2-((5-chloro-4-cyclopropoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.15-8.13 (d, *J*= 8.4 Hz, 1 H), 7.96 (s, 1 H), 7.71-7.67 (m, 1 H), 7.44-7.39 (m, 1 H), 5.80 (m, 1 H), 5.62-5.55 (m, 1 H), 5.05-5.01 (m, 1 H), 4.74-4.71 (m, 1 H), 4.64-4.50 (m, 1 H), 4.11-3.79 (m, 3 H), 2.91-2.88 (m, 1 H), 2.72-2.65 (m, 2 H), 2.43-2-37 (m, 2 H), 1.95-1.82 (m, 2 H), 1.81-1.70 (m, 2 H), 1.69-1.35 (m, 4 H), 1.34-1.20 (m, 4 H), 1.19-1.13 (m, 4 H), 1.12-1.03 (m, 9 H), 1.12-0.92 (m, 5 H), 0.92-0.8 (m, 4 H); MS: MS *m/z* 815.3 (M^++1).

Preparation of Compound 32

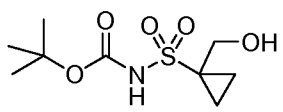


Compound 32

Compound 32 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

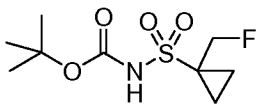
Compound 32: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-4-cyclopropoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17-8.15 (dd, *J*= 8.4 Hz & 1.2, 1 H), 8.0 (s*b*, 1 H), 7.76-7.74 (dd, *J*= 7.6 & 1.2 Hz, 1 H), 7.47-7.43 (t, *J* = 8 Hz, 1 H), 5.88 (m, 1 H), 5.64-5.60 (m, 1 H), 5.08-5.03 (m, 1 H), 4.81-4.76 (m, 1 H), 4.67-4.56 (m, 1 H), 4.0-3.94 (m, 2 H), 3.80-3.77 (m, 1 H), 2.94-2.72 (m, 1 H), 2.78-2-66 (m, 2 H), 2.48-2.32 (m, 2 H), 2.05-1.90 (m, 1 H), 1.89-1.77 (m, 3 H), 1.63-1.55 (m, 1 H), 1.53-1.42 (m, 2 H), 1.38-1.22 (m, 6 H), 1.20-1.06 (m, 3 H), 1.02-0.96 (m, 6 H), 0.94-0.90 (3 H), 0.9-0.8 (6 H); ^{19}F NMR: δ ppm -85.10 (3 F); MS: MS *m/z* 866.0 (M^+-2).

Preparation of tert-butyl (1-(hydroxymethyl)cyclopropyl)sulfonylcarbamate



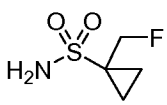
To a solution of tert-butyl cyclopropylsulfonylcarbamate (30 g, 136 mmol) in 750 mL of THF was added dropwise butyllithium (1.6 M in hexane, 212 mL, 339 mmol) over 30 min at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. Formaldehyde gas was generated from para-formaldehyde (by heating at 180 °C) and was purged in to the above reaction mass for 30 min at -30 °C. The reaction was stirred at the same temperature for 1 h, then allowed to warm to room temperature. The reaction was quenched with aqueous ammonium chloride solution and diluted with water. The resulting mass was washed with ethyl acetate and the aqueous layer was acidified to pH ~2 and extracted with ethyl acetate. The combined organics were dried over sodium sulfate and evaporated under reduced pressure to get desired compound (27 g, 79%) as white solid. . ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.90 (s*b*, 1H), 4.95 (sb, 1H), 3.75 (s, 2H), 1.42 (s, 9H), 1.27(m, 2H), 1.08 (m, 2 H).

Preparation of *tert-butyl 1-fluoromethylcyclopropylsulfonylcarbamate*



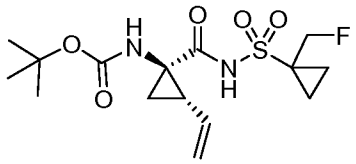
A solution of tert-butyl 1-hydroxymethylcyclopropylsulfonylcarbamate (26 g, 103 mmol) in DCM (300 mL) was cooled to -78 °C. To this solution was added DAST (41 mL, 310 mmol) and the reaction mass was stirred at the same temperature for 30 min. The reaction mass was quenched with aqueous 1N NaOH solutions. The organic layer was separated and the aqueous layer was acidified to pH ~ 2 by using 1.5 N HCl solutions. The aqueous solution was extracted with DCM (50 mL x 4). The combined organic layer was dried over anhydrous sodium sulphate and evaporated to get desired compound (19 g, 72%) as gummy mass. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 11.25 (s*b*, 1H), 4.75 (s, 1H), 4.63 (s, 1H), 1.44 (s, 9H), 1.28 (m, 2H), 1.07 (m, 2H). ^{19}F NMR: -211.7 (1F).

Preparation of *1-fluoromethylcyclopropane-1-sulfonamide:*



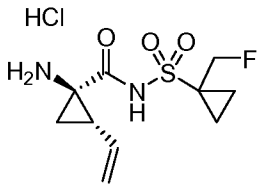
To a solution of tert-butyl 1-fluoromethyl cyclopropylsulfonylcarbamate (19 g, 75 mmol) in dichlomethane (200 mL) was added TFA (50 mL) at room temperature. The reaction mass was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure and the residue was diluted with hexane. The precipitated solid was filtered and washed with hexane to get pure compound (11 g, 96%) as off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 6.98 (s*b*, 2H), 4.75 (s, 1H), 4.63 (s, 1H), 1.28 (m, 2H), 1.08 (m, 2 H). ^{19}F NMR: -211.74 (1F).

Preparation of tert-butyl (1R,2S)-1-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamate



To a solution of (1R,2S)-1-(tert-butoxycarbonylamino)-2-vinylcyclopropanecarboxylic acid (7.5 g, 33 mmol) in DMF (50 mL) was added CDI (10.69 g, 66 mmol) and the reaction mass was heated at 55 °C for 4 h. To this reaction mass was added 1-fluoromethylcyclopropane-1-sulfonamide (6.5 g, 42.9 mmol) followed by DBU (6 mL, 42.9 mmol). The reaction mixture was stirred at 55 °C for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with water and acidified to pH ~ 2 by using 1.5 N HCl solution. The precipitated solid was filtered and washed with water to get desired compound (11.5 g, 96%) as off-white solid. MS: MS *m/z* 361.4 (M^+-1).

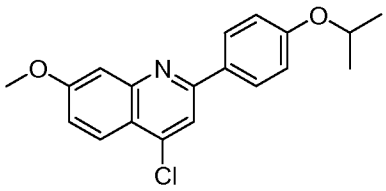
Preparation of *(1R,2S)-1-amino-N-(1-(fluoromethyl)cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride:*



A solution of *tert-butyl (1R,2S)-1-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamate* (11.5 g, 31.7 mmol) in 4 N HCl in dioxane (100 mL) was stirred at room temperature for 1 h.

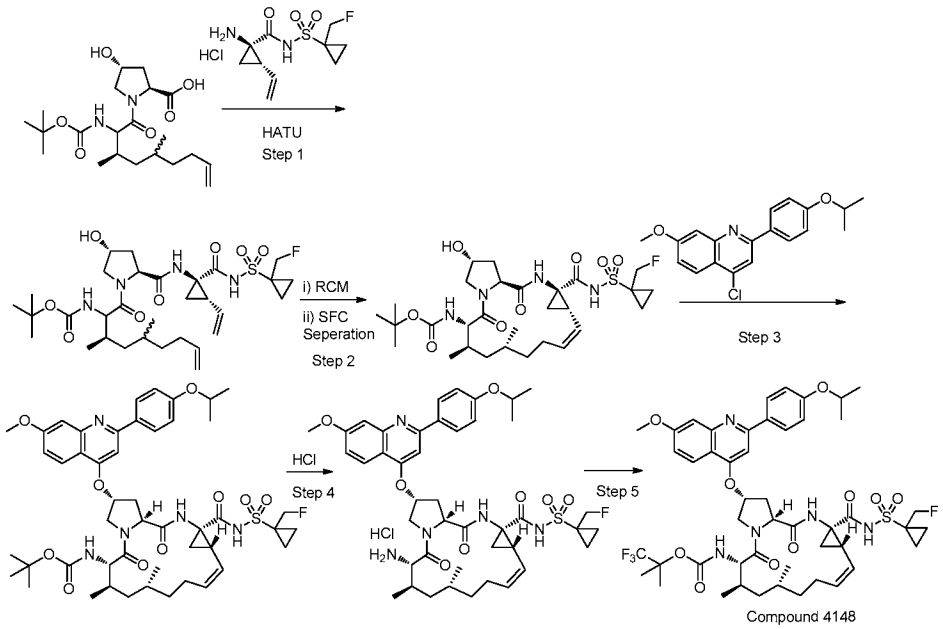
The solvent was evaporated under reduced pressure and the residue was washed with diethyl ether to get crude compound (6 g, 72%). The crude compound was taken to the next step without further purification. MS: MS *m/z* 263.14 (M^++1)

Preparation of 4-chloro-2-(4-isopropoxyphenyl)-7-methoxyquinoline

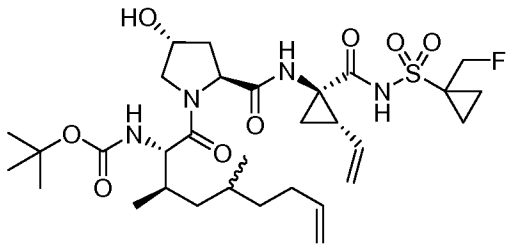


To a degassed solution of 2,4-dichloro-7-methoxyquinoline (1 g, 4.3 mmol) in dioxane/water (8:2) was added 4-isopropoxyphenylboronic acid (870 mg, 4.82 mmol) followed by potassium carbonate (1.2 g, 8.7 mmol) and $Pd(PPh_3)_4$ (253 mg, 0.22 mmol) at room temperature under nitrogen atmosphere. The reaction mass was heated at 90 °C for 18 h. The solvent was removed under reduced pressure and the residue was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to afford 4-chloro-2-(4-isopropoxyphenyl)-7-methoxyquinoline (1.2 g, 85%) as off white solid. MS: MS *m/z* 328.7 (M^++1).

Scheme



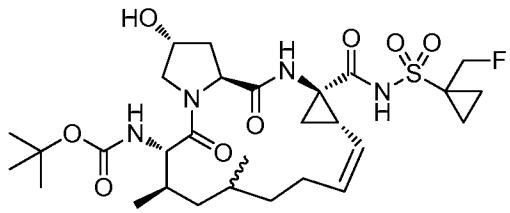
Step 1: Preparation of *tert-butyl (2S,3R)-1-((2S,4R)-2-((1R,2S)-1-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamoyl)-4-hydroxypyrrolidin-1-yl)-3,5-dimethyl-1-oxonon-8-en-2-ylcarbamate:*



To a solution of *(2S,4R)-1-((2S,3R)-2-(tert-butoxycarbonylamino)-3,5-dimethylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylic acid* (5.7 g, 13.82 mmol) in dichloromethane (60 mL) was added HATU (5.78 g, 15.2 mmole) followed by DIPEA (7.13 mL, 41.4 mmole) at room temperature. The reaction mass was stirred at the same temperature for 10 min. (1R,2S)-1-amino-N-(1-(fluoromethyl)cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride (4.34 g, 16.58 mmole) was added to the reaction mass and stirred at room temperature for 6 h. The reaction mass was diluted with dichloromethane and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude compound. The crude compound was purified by silica gel

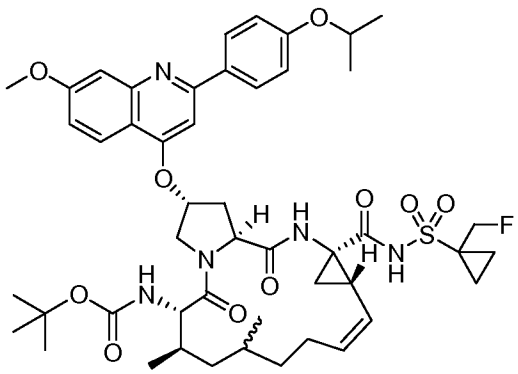
chromatography (5% methanol in chloroform) to get 6.6 g (73%) of desired product as white solid. MS: MS *m/z* 658.3 (M^++1).

Step 2: Preparation of tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-hydroxy-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate



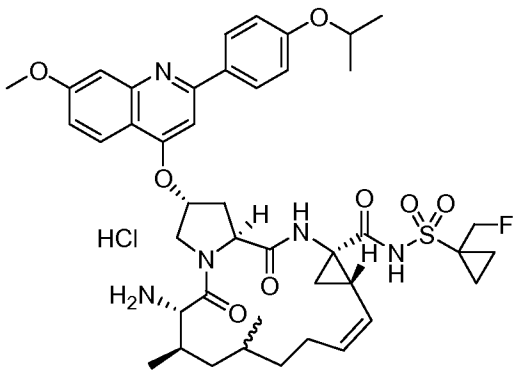
To a degassed solution of *tert-butyl (2S,3R)-1-((2S,4R)-2-((1R,2S)-1-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamoyl)-4-hydroxypyrrolidin-1-yl)-3,5-dimethyl-1-oxonon-8-en-2-ylcarbamate* (2.8 g, 4.26 mmole) in dichloroethane (200 mL) was added Grubbs II generation catalyst (280 mg) at room temperature under nitrogen atmosphere. The reaction mass was heated at 95 °C overnight. The solvent was evaporated under reduced pressure and the resulting residue was purified by silica gel chromatography (5% methanol in chloroform) to get desired compound *tert-butyl (2R,6S,7R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-hydroxy-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate* (1.87 g, 70%) as pale yellow crystalline solid. MS: MS *m/z* 629.3 (M^++1).

Step 3: *Preparation of tert-butyl (2R,6S,7R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(2-(4-isopropoxyphenyl)-7-methoxyquinolin-4-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate*



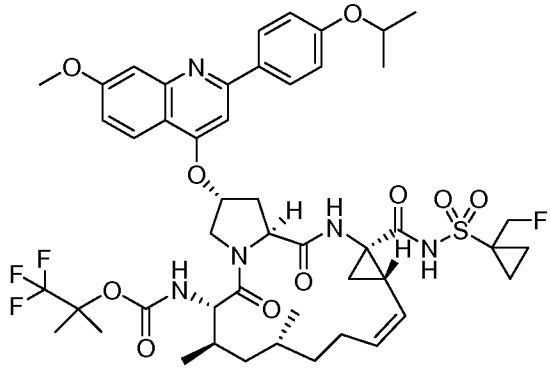
To a solution of tert-butyl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-hydroxy-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate (150 mg, 0.238 mmole) and 4-chloro-2-(4-isopropoxyphenyl)-7-methoxyquinoline (93 mg, 0.284 mmole) in DMSO (8 mL) was added *t*-BuOK (133 mg, 1.19 mmol, 1 M solution in THF, 1.2 mL) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mass was quenched with aqueous citric acid solution and extracted with ethyl acetate (10 mL x 2). The combined organic layer was washed with water, brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by HPLC to get 130 mg (60%) of desired compound *tert-butyl (2R,6S,7R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(2-(4-isopropoxyphenyl)-7-methoxyquinolin-4-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate* as white solid. MS: MS m/z 921.5 (M^++1).

Step 4*: Preparation of (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(1-(fluoromethyl)cyclopropylsulfonyl)-2-(2-(4-isopropoxyphenyl)-7-methoxyquinolin-4-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride*



A solution of tert-butyl (2R,6S,7R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(2-(4-isopropoxyphenyl)-7-methoxyquinolin-4-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate (130 mg, 0.14 mmole) was added to a solution of HCl in dioxane (4N, 5 mL) and the solution was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure to get crude compound. The crude compound was washed with diethyl ether to afford (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(1-(fluoromethyl)cyclopropylsulfonyl)-2-(2-(4-isopropoxyphenyl)-7-methoxyquinolin-4-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride (100 mg, 90%) as off-white solid. MS: MS *m/z* 821.3 (M^++1).

Step 5: Preparation of Compound 4148

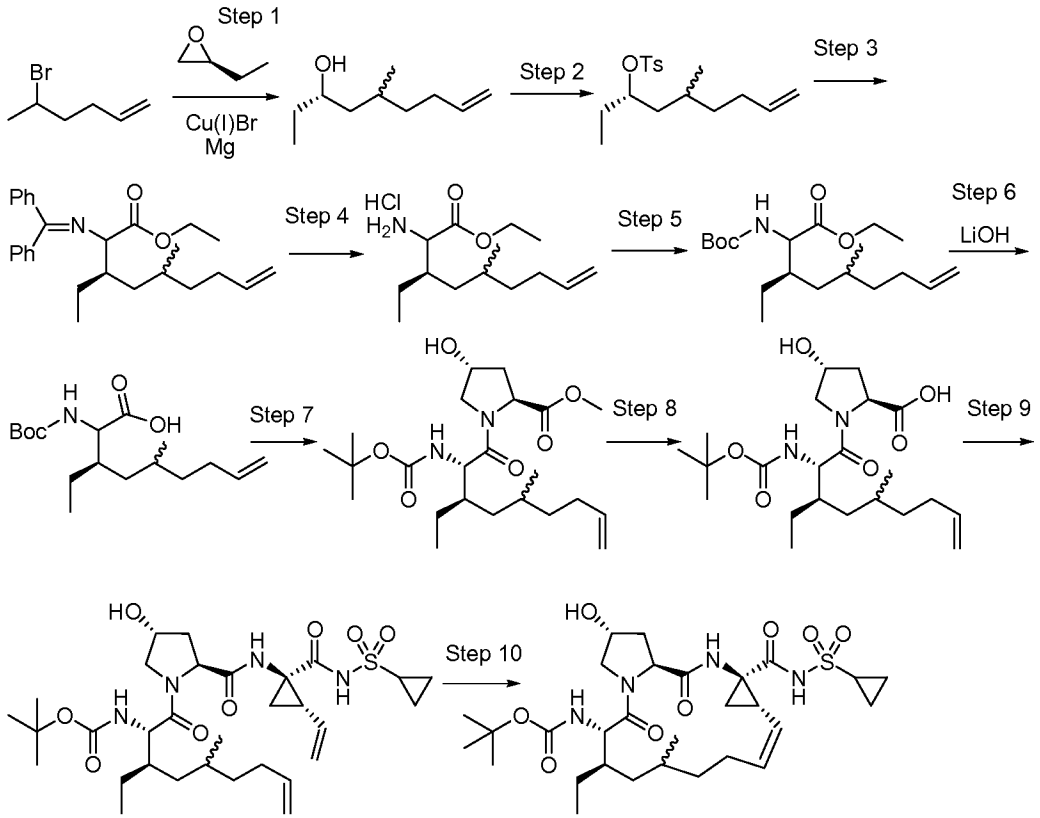


Compound 4148

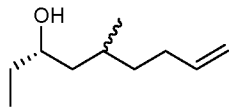
To a solution of *2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(1-(fluoromethyl)cyclopropylsulfonyl)-2-(2-(4-isopropoxyphenyl)-7-methoxyquinolin-4-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride* (100 mg, 0.16 mmol) in DCM (4 mL) was added DIPEA (0.06 mL, 0.48 mmole) followed by pyridin-2-yl (1,1,1-trifluoro-2-methylpropan-2-yl) carbonate (32.12 mg, 0.16 mmole) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The reaction mass was diluted with DCM and washed with water. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure to get crude compound. The crude compound was purified by HPLC to get Compound 4148 (30 mg, 26%) as a white solid.

Compound 4148: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((2-(4-isopropoxyphenyl)-7-methoxyquinolin-4-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.08-8.06 (d, *J*=9.2 Hz, 1H), 8.03-8.01 (d, *J*=8.8 Hz, 2H), 7.40-7.39 (m, 1H), 7.24 (s, 1H), 7.10-7.08 (d, *J*=8.8, Hz, 2H), 7.06 (m, 1 H), 5.62 (m, 2H), 4.92-4.84 (m, 1H), 4.77-7.73 (m, 2H), 4.64 -4.62 (m, 4H), 4.10 (m, 1H), 3.97 (s, 3H), 3.89-3.86 (m, 1H), 2.85-2.79 (m, 1H), 2.78-2.68 (m, 1H), 2.55-2.2.35 (m, 2H), 2.05-1.74 (m, 6H), 1.73-1.69 (m, 3H), 1.59 - 1.56 (m, 9H), 1.48 - 1.38 (m, 4H), 1.27 - 1.19 (m, 9H), 1.03-0.98 (m, 1H); MS: MS *m/z* 974.4 (M^++1).

Scheme:



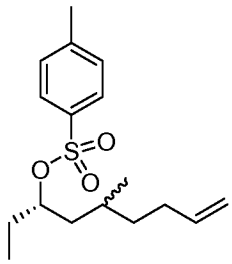
Step 1: Preparation of (S)-5-methylnon-8-en-3-ol



Magnesium turnings (3.03 g, 125 mmole) were taken in dry THF (100 mL) and was added a pinch of iodine (100 mg) at room temperature. To this reaction mass was added a solution of 5-bromohex-1-ene (20.37 g, 125 mmole) in THF (200 mL). The reaction mass was heated with hot air gun to initiate the reaction. This reagent was cannulated to a solution of (S)-2-ethyloxirane (6.05 g, 83 mmol) and copper bromide (1.19 g, 8.32 mmol) in THF (100 mL) at -78 °C. The reaction mass was allowed to come to room temperature and stirred for overnight. The reaction mass was quenched with saturated aqueous ammonium chloride solution and extracted with diethyl ether (200 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated at room temperature to get crude compound. The crude compound was purified by column chromotography (Silica gel, 10% TBME in pet

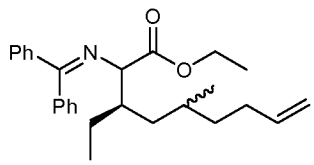
ether) to get *(S)-5-methylnon-8-en-3-ol* (9.5 g, 73.1%) as an oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 0.87-0.97 (m, 6 H), 1.22-1.32 (m, 4 H), 1.52-1.72 (m, 2 H), 1.90-2.29 (m, 2 H), 3.38-3.45 (m, 2 H), 4.16-4.19 (m, 1 H), 4.91-5.02 (m, 2 H), 5.75-5.82 (m, 1 H),

Step 2: Preparation of (S)-5-methylnon-8-en-3-yl 4-methylbenzenesulfonate



To a solution of *(S)-5-methylnon-8-en-3-ol* (9.5 g, 60.8 mmole) in DCM (100 mL) was added pyridine (20 mL) followed by DMAP (0.74 g, 6.08 mmole) and the solution was stirred for 10 min. p-Toluenesulfonyl chloride (17.39 g, 91 mmole) was added to the reaction mass at 0 °C. The reaction mass was allowed to come to room temperature and stirred for overnight. Solvent was removed under reduced pressure and the residue was diluted with ethyl acetate (100 mL). The organic solution was washed with aqueous 1.5 N HCl solution, saturated bicarbonate solution, brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound (15 g, 79%). The crude compound was taken to the next step without further purification. MS: MS *m/z* 328.4 (M^++18).

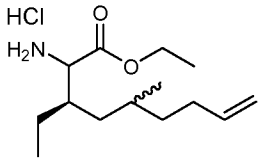
Step 3: Preparation of (3R)-ethyl 2-(diphenylmethyleneamino)-3-ethyl-5-methylnon-8-enoate



To a solution of *(S)-5-methylnon-8-en-3-yl 4-methylbenzenesulfonate* (15 g, 48.3 mmole) and *N*-(diphenylmethylene)glycinate ethyl ester (15.5 g, 58.0 mmole) in toluene (150 mL) was added LiHMDS (72.5 mL, 72.5 mmole, 1 M solution in THF) at 0 °C. The reaction mass was allowed to come to room temperature heated at 110 °C for 2 h. The reaction mass was cooled to room temperature, quenched with water

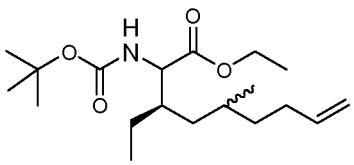
and extracted with ethyl acetate (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound (7.0 g, 35.7%). The crude compound was taken to the next step without further purification. MS: MS *m/z* 406.4 (M^++1).

Step 4: Preparation of (3R)-ethyl 2-amino-3-ethyl-5-methylnon-8-enoate hydrochloride



A solution of *(3R)-ethyl 2-(diphenylmethyleneamino)-3-ethyl-5-methylnon-8-enoate* (7 g, 17.26 mmole) in diethyl ether (20 mL) was added aqueous 1.5 N HCl solutions (100 mL) and the reaction mass was stirred at room temperature for overnight. The reaction mass was washed with diethyl ether (100 mL). The aqueous solution was basified using saturated sodium bicarbonate solution and extracted with ethyl acetate (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound (2.6 g, 62.4%). The crude compound was taken to the next step without further purification. MS: MS *m/z* 242.4 (M^++1).

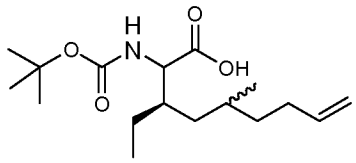
Step 5: Preparation of (3R)-ethyl 2-(tert-butoxycarbonylamino)-3-ethyl-5-methylnon-8-enoate



A solution of *(3R)-ethyl 2-amino-3-ethyl-5-methylnon-8-enoate hydrochloride* (2.99 g, 10.77 mmole) in DCM (20 mL) was added DIPEA (1.08 mL, 10.77 mmole) followed by $(BOC)_2O$ (2.39 mL, 10.77 mmole) at room temperature. The reaction mass was stirred at room temperature for overnight. The reaction mass was diluted with DCM and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromotography (Silica gel, 20% ethyl acetate in

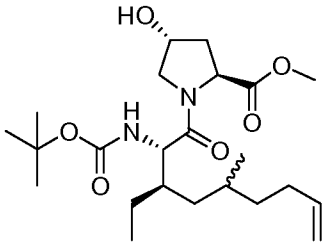
pet-ether) to get 2.3 g, (62.5%) of (3R)-ethyl 2-(tert-butoxycarbonylamino)-3,5-dimethylnon-8-enoate as an oily liquid. MS: MS *m/z* 342.4 (M^++1).

Step 6: Preparation of (3R)-2-(tert-butoxycarbonylamino)-3-ethyl-5-methylnon-8-enoic acid



To a solution of *(3R)-ethyl 2-(tert-butoxycarbonylamino)-3-ethyl-5-methylnon-8-enoate* (2.3 g, 6.74 mmole) in THF/water (50 mL, 1: 1) was added methanol (10 mL) followed by LiOH (0.84 g, 20.21 mmole) at room temperature. The reaction mass was stirred at room temperature for overnight. Solvent was evaporated under reduced pressure and the residue was diluted with water (10 mL). The aqueous solution was acidified with aqueous 1.5 N HCl solutions to pH ~3 and extracted with ethyl acetate (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduce pressure to get crude compound. The crude compound was purified by column chromotography (Silica gel, 2% methanol in DCM) to get 1.5 g (71%) of Intermediate 9 as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.27-1.09 (m, 8 H), 1.02-1.35 (m, 3 H), 1.39 (s, 11H), 1.91-1.97 (m, 1 H), 1.99-2.02 (m, 2 H), 4.03-4.12 (m, 1 H), 4.90-5.03 (m, 2 H), 5.74-5.84 (m, 1 H), 6.80-6.83 (m, 1 H), 12.47 (s*b*, 1 H).

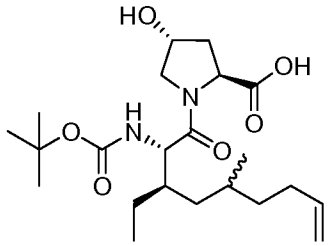
Step 7: Preparation of (2S,4R)-methyl 1-((2S,3R)-2-(tert-butoxycarbonylamino)-3-ethyl-5-methylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylate



To a solution of *(3R)-2-(tert-butoxycarbonylamino)-3-ethyl-5-methylnon-8-enoic acid* (2 g, 6.38 mmole) in dichloromethane (20 mL) was added DIPEA (1.93

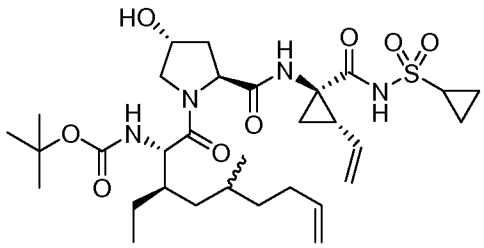
mL, 19.19 mmole), HATU (2.42 g, 6.38 mmole) followed by (2S,4R)-methyl 4-hydroxypyrrolidine-2-carboxylate (1.15 g, 6.38 mmole) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The reaction mass was diluted with DCM and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude compound. The crude compound was taken to the next step without further purification (1.5 g, 53.4%). MS: MS *m/z* 441.6 (M^++1).

Step 8: Preparation of (2S,4R)-1-((2S,3R)-2-(tert-butoxycarbonylamino)-3-ethyl-5-methylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylic acid



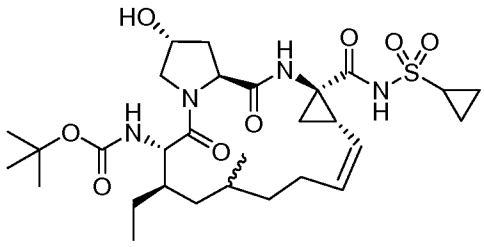
To a solution of *(2S,4R)-methyl 1-((2S,3R)-2-(tert-butoxycarbonylamino)-3-ethyl-5-methylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylate* (1.5 g, 3.40 mmole) in THF/water (16 mL, 1: 1) was added LiOH (286 mg, 6.80 mmole) followed by 3 mL of methanol at room temperature. The reaction mass was stirred at room temperature for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with water and acidified with aqueous 1.5 N HCl solutions. The aqueous solution was extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get desired product (1.3 g, 90%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 0.81-0.93 (m, 6 H), 1.12-1.29 (m, 5 H), 1.30-1.50 (m, 11H), 1.71-1.80 (m, 2 H), 1.91-2.51 (m, 4 H), 3.57-3.59 (m, 1H), 4.27-4.35 (m, 3 H), 4.92-4.97 (m, 2 H), 5.01-5.15 (m, 1 H), 5.74-5.79 (m, 1 H), 6.30-6.80 (m, 1 H), 12.50 (s*b*, 1 H). MS: MS *m/z* 427.6 (M^++1).

Step 9: Preperation of tert-butyl (2S,3R)-1-((2S,4R)-2-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamoyl)-4-hydroxypyrrolidin-1-yl)-3-ethyl-5-methyl-1-oxonon-8-en-2-ylcarbamate:



To a solution of *(2S,4R)-1-((2S,3R)-2-(tert-butoxycarbonylamino)-3-ethyl-5-methylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylic acid* (1.3 g, 3.05 mmole) in dichloromethane (50 mL) was added HATU (1.15 g, 3.05 mmole) followed by DIPEA (1.6 mL, 9.13 mmole) at room temperature. The reaction mass was stirred at the same temperature for 10 min. (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide (1.22 g, 3.05 mmole) was added to the reaction mass and was stirred at room temperature for 1 h. The reaction mass was diluted with dichloromethane and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude compound. The crude compound was purified by Silica gel chromatography (6% methanol in chloroform) to get 1.7 g (87%) of desired product as a white solid. MS: MS *m/z* 639.55 (M^++1).

Step 10: Preperation of tert-butyl (2R,6S,7R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-7-ethyl-2-hydroxy-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

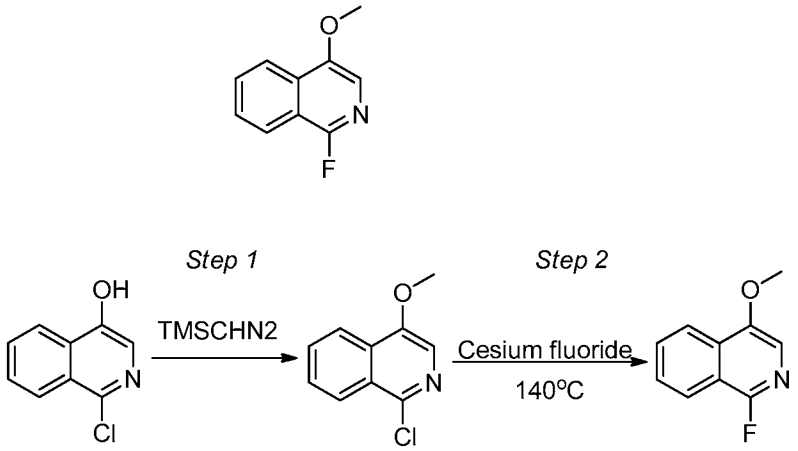


To a degassed solution of *tert-butyl (2S,3R)-1-((2S,4R)-2-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamoyl)-4-hydroxypyrrolidin-1-yl)-3-ethyl-5-methyl-1-oxonon-8-en-2-ylcarbamate* (1.7 g, 2.66 mmole) in dichloroethane (100 mL) was added Grubbs II generation catalyst (266 mg, 10% w/w) at room temperature under nitrogen atmosphere. The reaction mass was heated at 95 °C for overnight. The solvent was evaporated under reduced pressure and the

residue was purified by silica gel chromatography (5% methanol in chloroform) to get the desired compound (770 mg, 47.4%) as pale yellow crystalline solid. MS: MS *m/z* 609.20 (M^+-1).

Preparation of 1-Fluoro-4-methoxyisoquinoline

Synthesis of 1-fluoro-4-methoxyisoquinoline



Step 1: Preparation of 1-chloro-4-methoxyisoquinoline

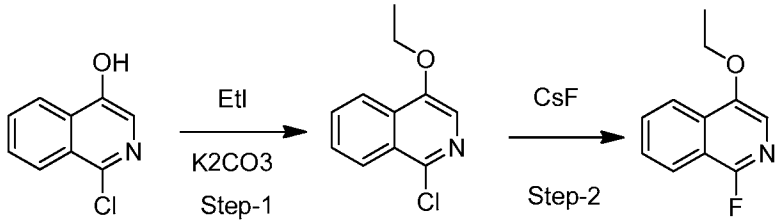
To a solution of 1-chloroisoquinolin-4-ol (5.0 g, 27.8 mmol) in acetonitrile (50 mL) was added TMS-diazomethane (12.73 g, 111.2 mmol) at 0 °C. The reaction mixture was allowed to come to room temperature and stirred for 2 h. Solvent was evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get 1-chloro-4-methoxyisoquinoline (2.5 g, 46.4%) as off-white solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.29-8.17 (m, 2H), 7.97 (s, 1H), 7.91-7.82 (m, 2H), 4.05 (s, 3H); MS: MS *m/z* 194.7 (M^++1).

Step 2: Preparation of 1-Fluoro-4-methoxyisoquinoline

To a solution of 1-chloro-4-methoxyisoquinolin (2.5 g, 12.91 mmol) in DMSO was added cesium fluoride (4.01 g, 25.82 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 145 °C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (700 mg, 62%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.10

(m, 1H), 8.08 (m, 1H), 7.78-7.75 (m, 1H), 7.69-7.65 (m, 1H), 7.49 (m, 1H), 4.04 (s, 3H); ^{19}F NMR: δ ppm -78.66 (1 F); MS: MS *m/z* 178.1 (M^++1).

Preparation of 1-fluoro-4-ethoxyisoquinoline



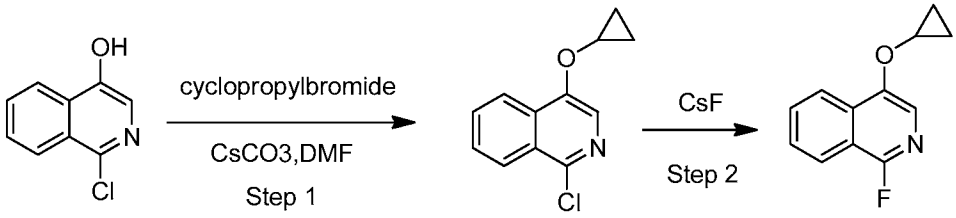
Step 1: Preparation of 1-chloro-4-ethoxyisoquinoline

To a solution of 1-chloroisoquinolin-4-ol (1.0 g, 5.5 mmol) in acetonitrile (10 mL) was added K_2CO_3 (2.3 g, 16.7 mmol) followed by ethyl iodide (0.87 ml, 11.0 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get 1-chloro-4-ethoxyisoquinoline (0.7 g, 62%) as off-white solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.26-8.24 (m, 2H), 7.79 (s, 1H), 7.76-7.26 (m, 2H), 4.29-4.24 (q, *J*= 6.8 Hz, 2H), 1.58-1.54 (t, *J*= 6.8 Hz, 3H); MS: MS *m/z* 207.7 (M^++1).

Step 2: Preparation of 1-Fluoro-4-ethoxyisoquinoline

To a solution of 1-chloro-4-ethoxyisoquinolin (4.8 g, 23.12 mmol) in DMSO was added cesium fluoride (6.9 g, 46.24 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 145°C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (2.6 g, 58.8%) as white solid. MS: MS *m/z* 192.3 (M^++1).

Scheme : Preparation of 1-fluoro-4-cyclopropoxyisoquinoline



Step 1: Preparation of 1-chloro-4-cyclopropoxyisoquinoline

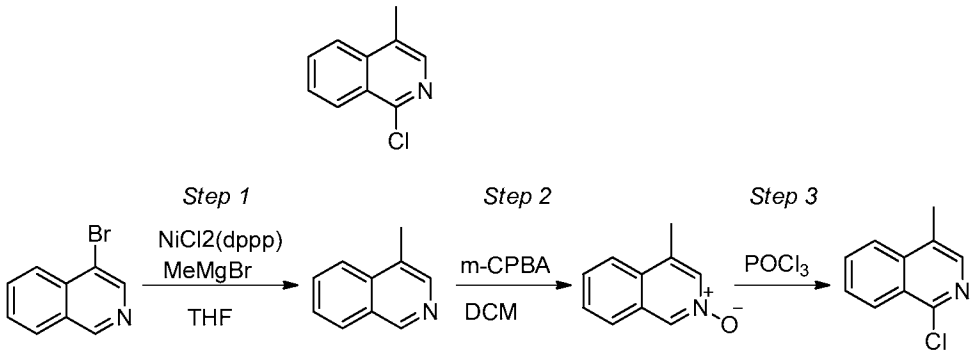
To a solution of 1-chloroisoquinolin-4-ol (1.0 g, 55.7 mmol) in DMF (20 m) was added Cs_2CO_3 (2.72 g, 8.35 mmol) followed by cyclopropylbromide (6.74 g, 55.7 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 145°C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (0.4 g, 32.7%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.22-8.24 (m, 2H), 8.14 (s, 1H), 8.14-8.12 (m, 1H), 7.74-7.67 (m, 2H), 4.00-3.95 (m, 1H), 0.92-0.90 (m, 4H); MS: MS *m/z* 220.0 (M^++1).

Step 2: Preparation of 1-Fluoro-4-cyclopropoxyisoquinoline

To a solution of 1-chloro-4-cyclopropoxyisoquinolin (2.3 g, 10.47 mmol) in DMSO (20 ml) was added cesium fluoride (6.36 g, 41.9 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 145°C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (0.8 g, 37.6%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.09-8.07 (m, 2H), 7.83 (s, 1H), 7.76-7.71 (m, 1H), 7.67-7.63 (m, 1H), 3.96-3.94 (m, 1H), 0.90-0.89 (m, 4H); ^{19}F NMR: δ ppm -78.58 (1 F); MS: MS *m/z* 204.2 (M^++1).

Scheme : Preparation of 1-Chloro-4-methylisoquinoline:

Synthesis of 1-Chloro-4-methylisoquinoline:



Step 1: Preparation of 4-methylisoquinoline

To a solution of 4-bromoisoquinoline (1 g, 4.81 mmol) in THF (20 ml) was added [1,3-Bis(diphenylphosphino)propane]nickel(II)chloride(0.026 g, 0.048 mmol) followed by methyl magnesium bromide in diethyl ether(1.923 ml, 5.77 mmol) at room temperature. The reaction mass was stirred at the same temperature for 18 h. The reaction mixture was acidified with 1N HCl and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (5% ethyl acetate in pet ether) to get desired compound (0.6 g, 78%) as an oil. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 9.15(s, 1H), 8.37 (s, 1H), 8.13-8.11 (d, *J* =8 Hz 1H), 8.05-8.03 (d, *J* =8 Hz, 1H), 7.83 (t, *J* =8 Hz, 1 H), 7.71 (t, *J* =8 Hz, 1 H) 2.59 (s, 3H); GC-MS: MS *m/z* 143 (M^+).

Step 2: Preparation of 4-methylisoquinoline 2-oxide

To a solution of 4-methylisoquinoline (0.6 g, 4.19 mmol) in DCM (20 ml) was added m-CPBA (2.169 g, 12.57 mmol) at room temperature. The reaction mass was stirred at the same temperature for 18 h. The reaction mass was diluted with DCM and extracted with water. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get desired compound (0.65 g, 88%) as a semi solid. The crude compound was taken further without purification.

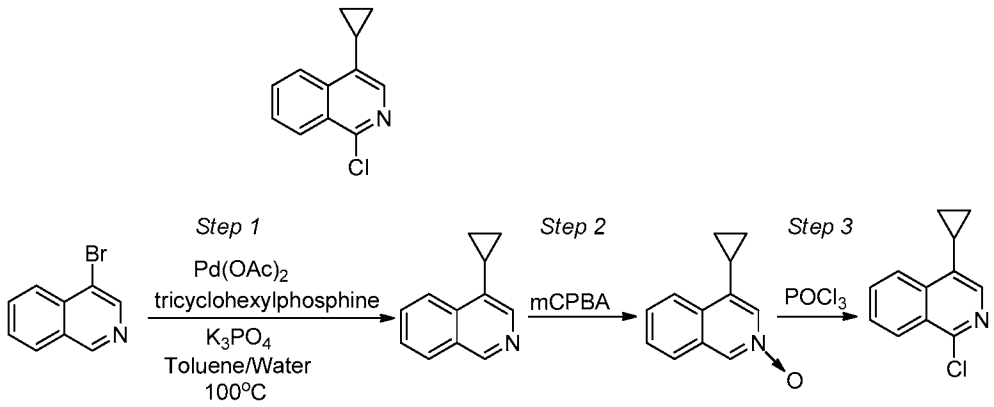
Step 3: Preparation of 1-chloro-4-methylisoquinoline

A solution of 4-methylisoquinoline 2-oxide (0.65 g, 4.08 mmol) in $POCl_3$ (6 ml) was refluxed for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified with solid

sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (10% ethyl acetate in pet ether) to get desired compound (0.17 g, 18.75%) as oil. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.14-8.12 (d, *J* =8 Hz, 1H), 7.97(s, 1H), 7.95-7.93 (d, *J* =8 Hz, 1 H), 7.86 (t, *J* =4 Hz, 1 H), 7. 84(t, *J* =8 Hz, 1 H), 2.59 (s, 3H); MS: MS *m/z* 178.2 (M^++1).

Scheme : Preparation of 1-Chloro-4-cyclopropylisoquinoline:

Synthesis of 1-Chloro-4-cyclopropylisoquinoline:



Step 1: Preparation of 4-cyclopropylisoquinoline

To a solution of 4-bromoisoquinoline (0.5 g, 2.403 mmol) and cyclopropylboronic acid(0.248 g, 2.88 mmol) in Toluene/water (11 ml, 10: 1) was added phosphoric acid, potassium salt(1.02 g, 4.81 mmol) followed by addition of tricyclohexylphosphine(0.067 g, 0.240 mmol) and palladium(II) acetate(0.027 g, 0.120 mmol). The reaction mass was heated 100 °C and stirred for overnight. The reaction mass was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (10% ethyl acetate in pet ether) to get desired compound (0.4 g, 93%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 9.12(s, 1H), 8.34-8.32(d, *J* =8 Hz, 1H), 8.31 (s, 1H), 7.98-7.96 (d, *J* =8 Hz, 1H), 7.76(t, *J*= 4 Hz, 1H), 7.62 (t, *J*= 4 Hz, 1H),2.23(s, 1H), 1.11(t, *J* =4 Hz, 2H), 0.82(t, *J* =8 Hz, 2H).

Step 2: Preparation of 4-cyclopropylisoquinoline-2-oxide

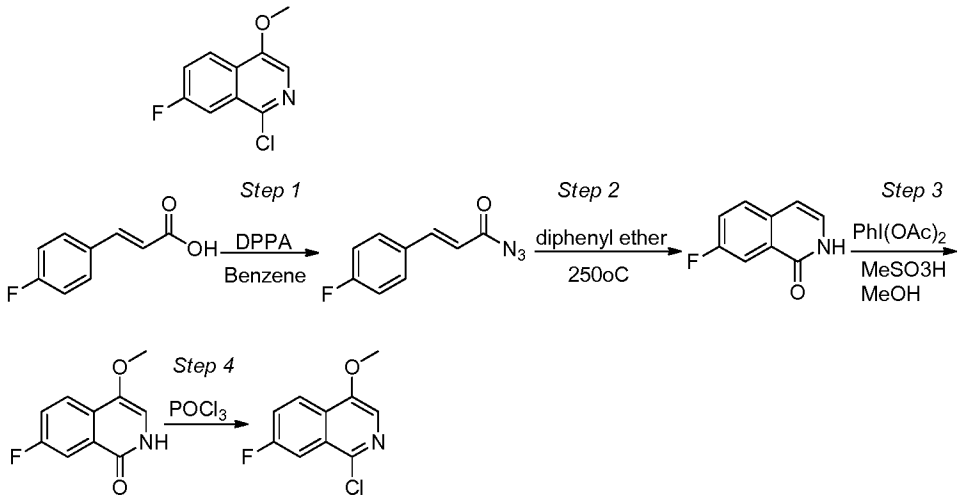
To a solution of 4-cyclopropylisoquinoline (0.4 g, 2.364 mmol) in DCM (10 ml) was added m-CPBA (1.224 g, 7.09 mmol) at room temperature. The reaction mass was stirred at the same temperature for 18 h. The reaction mass was diluted with DCM and washed with water and aqueou sodium bicarbonate solution. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get desired compound (0.35 g, 80%) as solid. The crude compound was taken further without purification.

Step 3: Preparation of 1-chloro-4-cyclopropylisoquinoline

A solution of 4-cyclopropylisoquinoline-2-oxide (0.3 g, 1.620 mmol) in $POCl_3$ (15 ml) was refluxed for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (10% ethyl acetate in pet ether) to get the desired compound (0.02 g, 5.76%) as oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.37-8.35(d, *J* =8 Hz, 2H), 8.08 (s, 1H), 7.81 (t, *J* =8 Hz, 1H), 7.70(t, *J*= 4 Hz, 1H), 2.18(m, 1H), 1.11(t, *J* =4 Hz, 2H), 0.80(t, *J* =8 Hz, 2H) ; MS: MS *m/z* 204.28 (M^++1).

Scheme: Preparation of 1-chloro-7-fluoro-4-methoxyisoquinoline

Synthesis of 1-Chloro-7-fluoro-4-methoxyisoquinoline:



Step 1: Preparation of (E)-3-(4-fluorophenyl) acryloyl azide

To a solution of (E)-3-(4-fluorophenyl) acrylic acid (25 g, 150 mmol) in benzene (120 mL) was added triethylamine (30.5 g, 301 mmol) followed by DPPA (41.4 g, 150 mmol) at room temperature. The reaction mass was stirred at the same temperature for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude compound. The crude compound was purified by conventional column chromatography (Silica gel, 60-120 mesh) using 10% ethyl acetate in pet ether as mobile phase to get the desired compound as a white solid (26 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.73-7.69 (d, J = 16 Hz, 1H), 7.55-7.51 (m, 2H), 7.11-7.07 (m, 2H), 6.36-6.32 (d, J = 16 Hz, 1H).

Step 2: Preparation of 7-fluoroisoquinolin-1(2H)-one

To a hot (125 °C) diphenyl ether (25 ml) was added (E)-3-(4-fluorophenyl) acryloyl azide (5g, 26.2 mmol) portion wise. The reaction was heated at 250°C for 4 h. The reaction mass was cooled to room temperature and diluted with pet ether. The precipitated solid was filtered washed with pet ether to get crude compound (2.45 g, 57%). The crude compound was taken to the next step without further purification. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.96-7.93 (m, 1H), 7.76-7.72 (m, 1H), 7.56-7.51 (m, 1H), 7.18-7.16 (m, 1H), 6.72-6.70 (m, 1H); MS: MS *m/z* 164.1 (M^++1).

Step 3: Preparation of 7-fluoro-4-methoxyisoquinolin-1(2H)-one

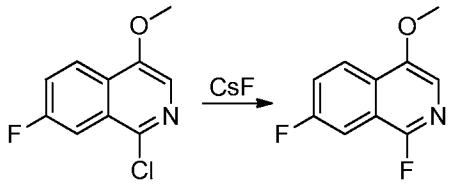
To a solution of 7-fluoroisoquinolin-1(2H)-one (11 g, 67.4 mmol) in methanol was added iodozobenzenediacetate (21.7 g, 67.4 mmol) followed by methane sulphonic acid (7.78 g, 81 mmol) at room temperature. The reaction mass was heated at reflux for 3 h. The solvent was evaporated and the residue was diluted with cold water. The precipitated solid was filtered and washed with water to get crude compound (11 g, 84%) as light red color solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.06-8.04 (m, 1H), 7.96-7.93 (m, 1H), 7.62-7.54 (m, 2H), 6.74 (s, 1H), 3.89 (s, 3H); MS: MS *m/z* 194.1 (M^++1).

Step 4: Preparation of 1-chloro-7-fluoro-4-methoxyisoquinoline

A solution of 7-fluoro-4-methoxyisoquinolin-1(2H)-one (11 g, 56.9 mmol) in $POCl_3$ (100 ml) was refluxed for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The combine organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get desired compound (2.9 g, 24%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.36-8.32 (m, 1H), 7.93-7.90 (m, 1H), 7.88 (s, 1H), 7.70-7.65 (m, 1H), 4.11 (s, 3H); MS: MS *m/z* 212.1 (M^++1).

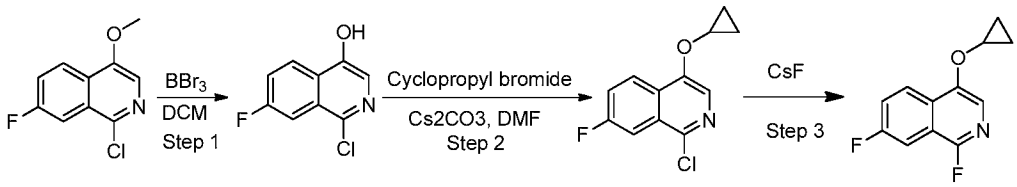
Scheme: Preparation of 1,7-difluoro-4-methoxyisoquinoline

Synthesis of 1, 7-Difluoro-4-methoxyisoquinoline:

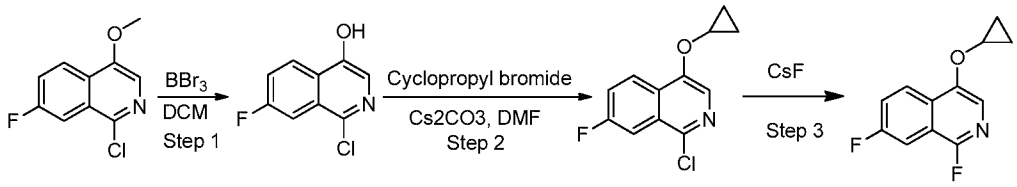


To a solution of 1-chloro-7-fluoro-4-methoxyisoquinoline (3.7 g, 17.48 mmol) in DMSO was added cesium fluoride (10.26 g, 69.9 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 145°C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (1.7 g, 49%) as white solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.20-8.18 (m, 1H), 7.69-7.66 (m, 1H), 7.54-7.47 (m, 1H), 7.46 (s, 1 H), 4.04 (s, 3H); ^{19}F NMR: δ ppm 109.65 (1F), -78.53 (1F); MS: MS *m/z* 196.1 (M^++1).

Scheme : Preparation of 1,7-diflouro-4cyclopropoxyisoquinoline



Scheme : Preparation of 1,7-diflouro-4cyclopropoxyisoquinoline



Step 1: Preparation of 1-chloro-7-flouro-4-hydroxyisoquinoline

A solution of 1-chloro-7-flouro-4-methoxyisoquinoline (0.75 g, 3.54 mmol) in DCM (10 ml) was added BBr_3 (6.22 g, 24.81 mmol) at 0°C drop wise. The reaction mass was refluxed for 5 h. The residue was cooled and quenched with methanol. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The precipitated solid was filtered, washed with water to get crude compound (0.65 g, 93%) as a pale yellow solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.36-8.33 (m, 1H), 7.89-7.86 (d, *J* = 12 Hz, 1H), 7.76 (s, 1H), 7.64 (t, *J* = 10 Hz, 1H); MS: MS *m/z* 198.0 (M^++1).

Step 2: Preparation of 1-chloro-7-flouro-4-cyclopropoxyisoquinoline

To a solution of 1-chloro-7-flouroisoquinolin-4-ol (1 g, 5.06 mmol) in DMF (5 mL) was added Cs_2CO_3 (4.95 g, 15.18 mmol) followed by cyclopropyl bromide (1.2 mL, 15.18 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 145°C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (0.24 g, 20%) as a yellow solid.

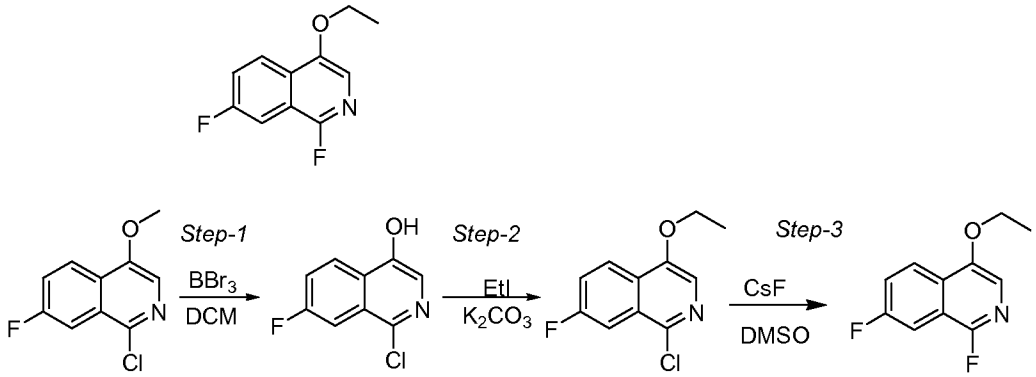
Step 3: Preparation of 1, 7-difluoro-4-cyclopropoxyisoquinoline

To a solution of 1-chloro-7-flouro-4-cyclopropoxyisoquinolin (0.24 g, 1.01

mmol) in DMSO (2 ml) was added cesium fluoride (0.38 g 2.52 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 145°C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (0.15 g 67%) as a white solid.

Scheme: Preparation of 1-Fluoro-4-ethoxy-7-fluoroisoquinoline

Synthesis of 1-Fluoro-4-ethoxy-7-fluoroisoquinoline:



Step 1: Preparation of 1-chloro-7-flouro-4-hydroxyisoquinoline

A solution of 1-chloro-7-flouro-4-methoxyisoquinoline (0.75 g, 3.54 mmol) in DCM (10 ml) was added BBr_3 (6.22 g, 24.81 mmol) at 0°C drop wise. The reaction mass was refluxed for 5 h. The residue was cooled and quenched with methanol. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The precipitated solid was filtered, washed with water to get crude compound (0.65 g, 93%) as pale yellow solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.36-8.33 (m, 1H), 7.89-7.86 (d, J = 12 Hz, 1H), 7.76 (s, 1H), 7.64 (t, J = 10 Hz, 1H); MS: MS *m/z* 198.0 (M^++1).

Step 2: Preparation of 1-chloro-7-flouro-4-ethoxyisoquinoline

To a solution of 1-chloro-7-flouroisoquinolin-4-ol (0.5 g, 2.53 mmol) in acetonitrile (10 ml) was added K_2CO_3 (700 mg, 5.06 mmol) followed by ethyl iodide (475 mg, 3.04 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with ethyl acetate. The combined

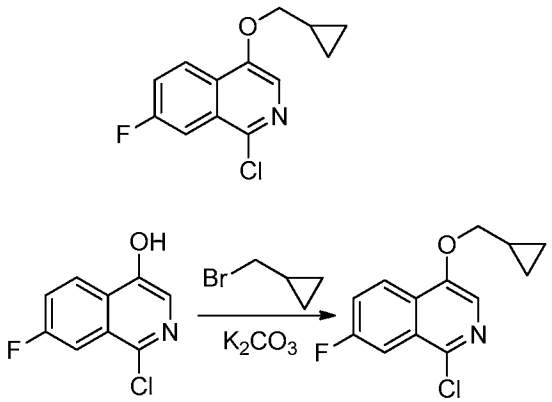
organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get 1-chloro-7-flouro-4-ethoxyisoquinoline (400 mg 70%) as off-white solid.

Step3: Preparation of 1, 7-difluoro-4-ethoxyisoquinoline

To a solution of 1-chloro-4-ethoxyisoquinolin (0.2 g, 0.88 mmol) in DMSO (2 mL) was added cesium fluoride (0.37 g, 2.21 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 145°C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (120 mg, 65%) as white solid. MS: MS *m/z* (M^++1).

Scheme: Preparation of 1-chloro-7-flouro-4-cyclopropylmethoxyisoquinoline

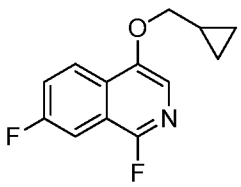
Synthesis of 1-Chloro-4-(cyclopropylmethoxy)-7-fluoroisoquinoline:



To a solution of 1-chloro-7-flouro-4-hydroxyisoquinoline (1.0 g, 5.06 mmol) in acetonitrile (10 ml) was added K_2CO_3 (2 g, 15.18 mmol) followed by cyclopropylmethylbromide (1.36 g, 10.12 mmol) at room temperature. The reaction mixture was heated to 50°C for 2 hr. Solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get 1-chloro-4-ethoxyisoquinoline (0.7 g, 55%) as pale yellow

solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.38-8.34 (q, *J* = 8 Hz, 1H), 7.89-7.86 (d, *J* = 12 Hz, 1H), 7.81 (s, 1H), 7.65 (t, *J* = 10 Hz, 1H), 4.11-4.09 (d, *J* = 8 Hz, 2H), 1.43-1.37 (m, 1H), 0.72-0.67 (m, 2H), 0.46-0.39 (m, 2H) ; MS: MS *m/z* 252.0 (M^++1).

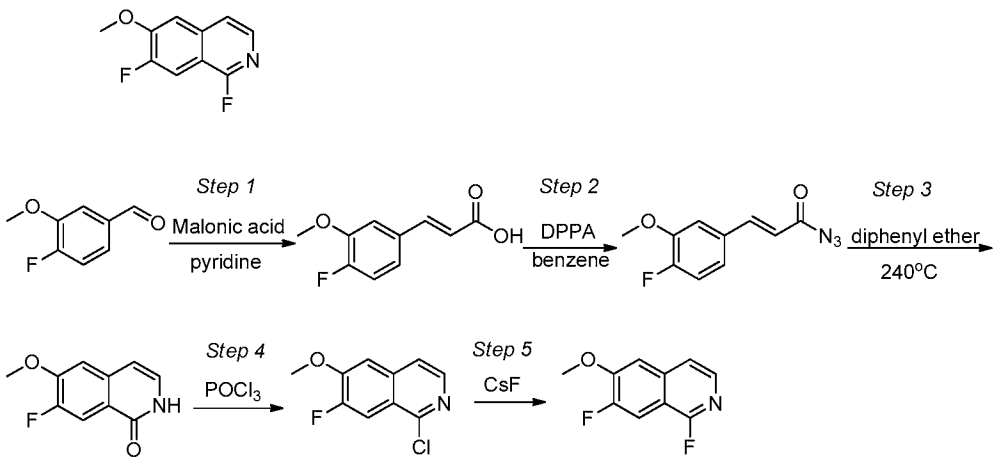
Preparation of 1, 7-difluoro-4-cyclopropylmethoxyisoquinoline



To a solution of 1-Chloro-4-(cyclopropylmethoxy)-7-fluoroisoquinoline (0.7 g, 2.78 mmol) in DMSO (5 mL) was added cesium fluoride (1.0 g, 6.95 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 145°C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (0.43 g, 65%) as white solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.35-8.33 (m, 1H), 7.77-7.74 (d, *J* = 12 Hz, 1H) 7.73 (t, *J* = 8 Hz, 1H), 7.52-7.51 (d, *J* = 4 Hz, 1H), 4.10-4.08 (d, *J* = 8 Hz, 2H), 1.42-1.40 (m, 1H), 0.74-0.69 (m, 2H), 0.49-0.46 (m, 2H) ;MS: MS *m/z 237.0* (M^++1).

Scheme: Preparation of 1,7-difluoro-6-methoxyisoquinoline

Synthesis of 1,7-difluoro-6-methoxyisoquinoline:



Step 1: Preparation of (E)-3-(4-fluoro-3-methoxyphenyl) acrylic acid

To a solution of 4-fluoro-3-methoxybenzaldehyde (30 g, 195 mmol) in pyridine (134 ml) and Piperidine (4.12 ml) was added malonic acid (30.4 g, 292 mmol) at room temperature. The reaction mass was refluxed for 18 h. The solvent was evaporated under reduced pressure and the residue was acidified with 1.5N HCl solution. The precipitated solid was filtered washed with pet ether to get crude compound (37 g, 97%) as white solid. The crude compound was taken to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.37 (s, 1H), 7.59-7.55 (d, *J* = 16 Hz, 1H), 7.53 (s, 1H), 7.26-7.22 (m, 2H), 6.59-6.55 (d, *J* = 16 Hz, 1H), 3.89 (s, 3H); MS: MS *m/z* 195.0 (M^+-1).

Step 2: Preparation of (E)-3-(4-fluoro-3-methoxyphenyl) acryloyl azide

To a solution of (E)-3-(4-fluoro-3-methoxyphenyl) acrylic acid (5 g, 25.5 mmol) in benzene (30 ml) was added triethylamine (5.16 g, 51 mmol) followed by DPPA (7.01 g, 25.5 mmol) at room temperature. The reaction mass was stirred at the same temperature for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude compound. The crude compound was purified by conventional column chromatography (Silica gel, 60-120 mesh) using 10% ethyl acetate in pet ether as mobile phase to get the desire compound as white solid (4 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.70-7.66 (d, *J* = 16 Hz, 1H), 7.12-7.07 (m, 3H), 6.35-6.31 (d, *J* = 16 Hz, 1H), 3.92 (s, 3H).

Step 3: Preparation of 7-fluoro-6-methoxyisoquinolin-1(2H)-one

To a hot (125 °C) diphenyl ether (20 ml) was added (E)-3-(4-fluoro-3-methoxyphenyl) acryloyl azide (4 g, 18.08 mmol) portion wise. The reaction was heated at 250°C for 4 h. The reaction mass was cooled to room temperature and diluted with pet ether. The precipitated solid was filtered washed with pet ether to get crude compound (3.1 g, 89%). The crude compound was taken to the next step without further purification. MS: MS *m/z* 194.1 (M^++1).

Step 4: Preparation of 1-chloro-7-fluoro-6-methoxyisoquinoline

A solution of 7-fluoro-6-methoxyisoquinolin-1(2H)-one (3.1 g, 16.05 mmol) in $POCl_3$ (25 ml) was refluxed for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was

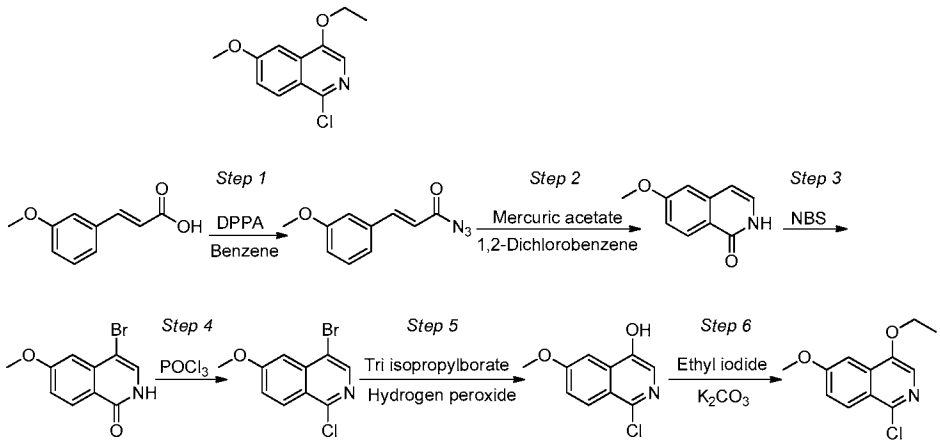
basified by solid sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get desired compound (1.9 g, 55%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.22-8.20 (d, J = 8 Hz, 1H), 7.97-7.94 (m, 1H), 7.49-7.48 (m, 1H), 7.18-7.16 (d, J =8 Hz, 1 H), 4.04 (s, 3H); MS: MS *m/z* 211.7 (M^++1).

Step 5: Preparation of 1,7-difluoro-6-methoxyisoquinoline

To a solution of 1-chloro-7-fluoro-6-methoxyisoquinoline (1.5 g, 7.09 mmol) in DMSO was added cesium fluoride (2.15 g, 14.18 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 145°C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (950 mg, 68%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.0-7.98 (m, 1H), 7.77-7.74 (d, J = 12 Hz, 1H), 7.42-7.40 (m, 1H), 7.21-7.19 (m, 1H), 4.04 (s, 3H); ^{19}F NMR: δ ppm -129.05 (1 F), -71.98 (1F); MS: MS *m/z* 196.1 (M^++1).

Scheme: Preparation of 1-Chloro-4-ethoxy- 6-methoxyisoquinoline

Synthesis of 1-Chloro-4-ethoxy- 6-methoxyisoquinoline:



Step 1: Preparation of (E)-3-(3-methoxyphenyl)acryloyl azide

To a solution of (E)-3-(3-methoxyphenyl)acrylic acid (15 g, 84 mmol) in benzene (100 ml) was added triethylamine (11.73 ml, 84 mmol) followed by DPPA

(23.17 g, 84 mmol) at room temperature. The reaction mass was stirred at the same temperature for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude compound. The crude compound was purified by conventional column chromatography (Silica gel, 60-120 mesh) using 10% ethyl acetate in pet ether as mobile phase to get the desire compound as white solid (15 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.75-7.70 (d, *J* = 20 Hz, 1H), 7.36-6.97 (m, 4H), 6.45-6.40 (d, *J* = 20 Hz, 1H), 3.85 (s, 3H).

Step 2: Preparation of 6-methoxyisoquinolin-1(2H)-one

To a solution of (E)-3-(3-methoxyphenyl)acryloylazide (2.0 g, 9.84 mmol) in 1,2-dichlorobenzene(10 ml) was added mercuric acetate(0.031 g, 0.098 mmol). The reaction was heated at 120 °C and stirred for 5 minutes at this temperature and then it was heated to 180 °C for 1 h. The reaction mass was cooled to room temperature and diluted with pet ether. The precipitated solid was filtered washed with pet ether to get crude compound (1.2 g, 69.6%). The crude compound was taken to the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 11.03 (s, 1H), 8.08-8.06 (d, *J* =8 Hz, 1H), 7.14-7.03 (m, 3H), 6.48-6.46 (d, *J* =8 Hz, 1H), 3.87 (s, 3H); MS: MS *m/z* 176.1 (M^++1).

Step 3: Preparation of 4-bromo-6-methoxyisoquinolin-1(2H)-one

To a solution of 6-methoxyisoquinolin-1(2H)-one (2.5 g, 14.27 mmol) in acetonitrile (10 ml) was added NBS (2.54 g, 14.27 mmol) at room temperature under argon atmosphere. The reaction mass was stirred at the same temperature for 2 hr. The precipitated solid was filtered to get crude compound (2 g, 55.2%). The crude compound was taken to the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 11.41 (s, 1H), 8.17-8.15 (d, *J* =8 Hz, 1H), 7.53 (s, 1H), 7.19-7.11 (m, 2H), 3.93 (s, 3H); MS: MS *m/z* 256.06 (M^++2).

Step 4: Preparation of 4-bromo-1-chloro-6-methoxyisoquinoline

A solution of 4-bromo-6-methoxyisoquinolin-1(2H)-one (1.5 g, 5.90 mmol) in $POCl_3$ (15 ml) was refluxed for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The combine

organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (10% ethyl acetate in pet ether) to get desired compound (1.1 g, 65%) as white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.53(s, 1H), 8.27-8.24 (d, *J* =12 Hz, 1H), 7.56-7.53 (d, *J* =12 Hz, 1H), 7.41(s, 1H), 4.02(s, 3H); MS: MS *m/z* 273.99 (M^++1).

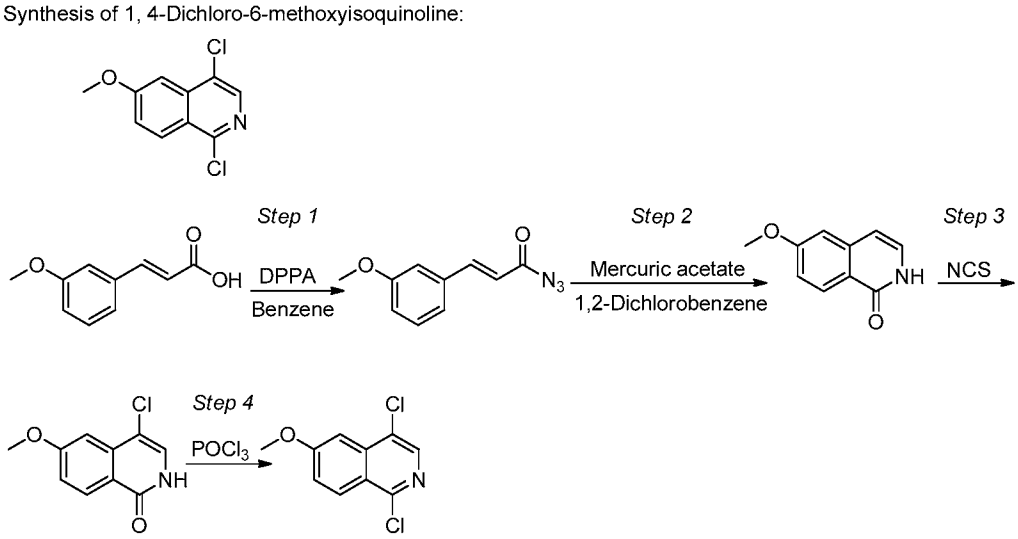
Step 5: Preparation of 1-chloro-6-methoxyisoquinolin-4-ol

To a solution of 4-bromo-1-chloro-6-methoxyisoquinoline (0.25 g, 0.917 mmol) in THF (30 ml) was added n-Butyl Lithium (1.147 ml, 1.835 mmol) at -78 °C under nitrogen. The reaction mixture was stirred for 30 minutes and Triisopropyl borate (0.426 ml, 1.835 mmol) was added and stirred for another 30 minutes. To this Hydrogen Peroxide (0.273 ml, 8.90 mmol) (30% solution 1.5M) was added followed by the addition of sodium hydroxide (0.917 ml, 0.917 mmol). The resulting mixture was stirred for additional 1 h at room temperature. The reaction mixture was cooled to -40 °C and added sodium sulfite solution in water (1.156 g, 9.17 mmol). The resulting slurry was neutralized with 6N HCl solution and extracted with ethyl acetate. The combine organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get desired compound (0.13 g, 67.6%) as solid. MS: MS *m/z* 210.06 (M^++1).

Step 6: Preparation of 1-chloro-4-ethoxy-6-methoxyisoquinoline

To a solution of 1-chloro-6-methoxyisoquinolin-4-ol (0.05 g, 0.239 mmol) in acetonitrile(5 ml) was added potassium carbonate (0.099 g, 0.716 mmol) followed by iodoethane (0.039 ml, 0.477 mmol) at room temperature. The reaction mass was stirred at the same temperature for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude compound. The crude compound was purified by silica gel chromatography (10% ethyl acetate in pet ether) to get desired compound (0.015 g, 25.1%) as solid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.14-8.12 (d, *J* = 8 Hz, 1H), 7.90 (s, 1H), 7.46-7.42 (m, 2H), 4.34-4.27(q, *J* = 8 Hz, 2H), 3.95 (s, 3H), 1.48(t, *J* = 10 Hz, 3H).

Scheme: Preparation of 1,4-dichloro-6-methoxyisoquinoline



Step 1: Preparation of (E)-3-(3-methoxyphenyl)acryloyl azide

To a solution of (E)-3-(3-methoxyphenyl)acrylic acid (15 g, 84 mmol) in benzene (100 ml) was added triethylamine (11.73 ml, 84 mmol) followed by DPPA (23.17 g, 84 mmol) at room temperature. The reaction mass was stirred at the same temperature for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with water follwed by extraction with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude compound. The crude compound was purified by conventional column chromatography (Silica gel, 60-120 mesh) using 10% ethyl acetate in pet ether as mobile phase to get the desire compound as white solid (15 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.75-7.70 (d, J = 20 Hz, 1H), 7.36-6.97 (m, 4H), 6.45-6.40 (d, J = 20 Hz, 1H), 3.85 (s, 3H).

Step 2: Preparation of 6-methoxyisoquinolin-1(2H)-one

To a solution of (E)-3-(3-methoxyphenyl) acryloylazide (2.0 g, 9.84 mmol) in 1,2-dichlorobenzene(10 ml) was added mercuric acetate(0.031 g, 0.098 mmol). The reaction was heated at 120 °C and stirred for 5 minutes at this temperature and then it was heated to 180 °C for 1 h. The reaction mass was cooled to room temperature and diluted with pet ether. The precipitated solid was filtered and washed with pet ether to get crude compound (1.2 g, 69.6%). The crude compound was taken to the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 11.03 (s,

1H), 8.08-8.06 (d, *J* =8 Hz, 1 H), 7.14-7.03 (m, 3H), 6.48-6.46 (d, *J* =8 Hz, 1H), 3.87 (s, 3H); MS: MS *m/z* 176.1 (M^++1).

Step 3: Preparation of 4-chloro-6-methoxyisoquinolin-1(2H)-one

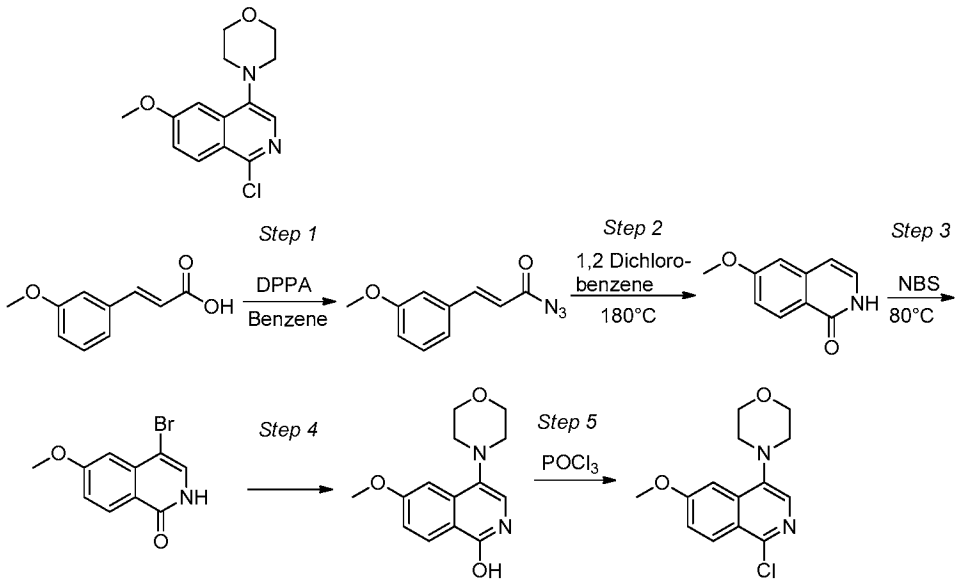
To a solution of 6-methoxyisoquinolin-1(2H)-one (2.5 g, 14.27 mmol) in acetonitrile (10 ml) was added NCS (2.54 g, 14.27 mmol) at 80 °C for overnight. The reaction mass was cooled to room temperature and the precipitated solid was filtered to get crude compound (2 g, 55.2%). The crude compound was taken to the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 11.41 (s, 1H), 8.17-8.15 (d, *J* =8 Hz, 1H), 7.53 (s, 1H), 7.19-7.11 (m, 2H), 3.93 (s, 3H); MS: MS *m/z* 210.02 (M^++1).

Step 4: Preparation of 1, 4-dichloro-6-methoxyisoquinoline

A solution of 4-chloro-6-methoxyisoquinolin-1(2H)-one (1.5 g, 5.90 mmol) in $POCl_3$ (15 ml) was refluxed for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The combine organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (10% ethyl acetate in pet ether) to get desired compound (1.1 g, 65.0%) as white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.53(s, 1H), 8.27-8.24 (d, *J* =12 Hz, 1 H), 7.56-7.53 (d, *J* =12 Hz, 1 H), 7.41(s, 1H), 4.02(s, 3H); MS: MS *m/z* 230.03 (M^++2).

Scheme: Preparation of 4-(1-Chloro-6-methoxy isoquinoline-4-yl) morpholine & 4-(1-Chloro-6-methoxy isoquinoline-4-yl) -2, 6-dimethyl morpholine

Synthesis of 4-(1-Chloro-6-methoxy isoquinoline-4-yl) morpholine :



Step 1: Preparation of (E)-3-(3-methoxyphenyl)acryloyl azide

To a solution of (E)-3-(3-methoxyphenyl)acrylic acid (15 g, 84 mmol) in benzene (100 ml) was added triethylamine (11.73 ml, 84 mmol) followed by DPPA (23.17 g, 84 mmol) at room temperature. The reaction mass was stirred at the same temperature for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude compound. The crude compound was purified by conventional column chromatography (Silica gel, 60-120 mesh) using 10% ethyl acetate in pet ether as mobile phase to get the desire compound as a white solid (15 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.75-7.70 (d, J = 20 Hz, 1H), 7.36-6.97 (m, 4H), 6.45-6.40 (d, J = 20 Hz, 1H), 3.85 (s, 3H).

Step 2: Preparation of 6-methoxyisoquinolin-1(2H)-one

To a solution of (E)-3-(3-methoxyphenyl)acryloyl azide (2.0 g, 9.84 mmol) in 1,2-dichlorobenzene (10 ml) was added mercuric acetate(0.031 g, 0.098 mmol). The reaction was heated at 120 °C and stirred for 5 minutes at this temperature and then it was heated to 180 °C for 1 h. The reaction mass was cooled to room temperature and diluted with pet ether. The precipitated solid was filtered washed with pet ether to get

crude compound (1.2 g, 69.6%). The crude compound was taken to the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 11.03 (s, 1H), 8.08-8.06 (d, *J* =8 Hz, 1H), 7.14-7.03 (m, 3H), 6.48-6.46 (d, *J* =8 Hz, 1H), 3.87 (s, 3H); MS: MS *m/z* 176.1 (M^++1).

Step 3: Preparation of 4-bromo-6-methoxyisoquinolin-1(2H)-one

To a solution of 6-methoxyisoquinolin-1(2H)-one (2.5 g, 14.27 mmol) in acetonitrile (10 ml) was added NBS (2.54 g, 14.27 mmol) at room temperature under argon atmosphere. The reaction mass was stirred at the same temperature for 2 h. The precipitated solid was filtered to get crude compound (2 g, 55.2%). The crude compound was taken to the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 11.41 (s, 1H), 8.17-8.15 (d, *J* =8 Hz, 1H), 7.53 (s, 1H), 7.19-7.11 (m, 2 H), 3.93 (s, 3H); MS: MS *m/z* 256.06 (M^++2).

Step 4: Preparation of 6-methoxy-4-morpholinoisoquinolin-1-ol

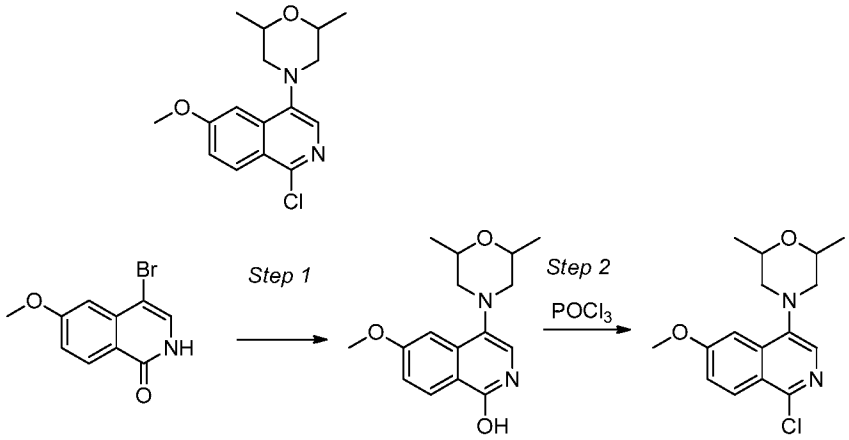
To a solution of 4-bromo-6-methoxyisoquinolin-1(2H)-one *(0.5 g,* 1.968 mmol) and morpholine (0.429 g, 4.92 mmol*)* in ethylene glycol (2.5 ml) was added DIPEA (1.031 ml, 5.90 mmol). The reaction was irradiated in a microwave at 145 °C for 1.5 h. The reaction mixture was adsorbed on silica was purified by silica gel chromatography (30% ethyl acetate in pet ether) to get desired compound (0.29 g, 53.8%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.98(s, 1H), 8.11(s, 1H), 7.24-7.11(m, 3H), 3.88 (s, 3H), 3.56-3.55 (m, 4H), 2.52-2.51(m, 4H); MS: MS *m/z* 261 (M^++1).

Step 5: Preparation of 4-(1-chloro-6-methoxyisoquinolin-4-yl) morpholine

A solution of 6-methoxy-4-morpholinoisoquinolin-1-ol (0.33 g, 1.268 mmol) in $POCl_3$ (5 ml) was refluxed for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The combine organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (10% ethyl acetate in pet ether) to get desired compound (0.065 g, 18%) as oil. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.18-8.16(d, *J* =8 Hz 1H), 7.94 (s, 1H), 7.45-7.40 (m, 2H), 3.98(s, 3H), 3.88-3.86(m, 4H), 3.09-3.07(m, 4H); MS: MS *m/z* 279.1 (M^++1).

Scheme: Preparation of 4-(1-Chloro-6-methoxy isoquinoline-4-yl) -2, 6-dimethyl morpholine

Synthesis of 4-(1-Chloro-6-methoxy isoquinoline-4-yl) -2, 6-dimethyl morpholine:



Step 1: Preparation of 4-(2,6-dimethylmorpholino)-6-methoxyisoquinolin-1(2H)-one

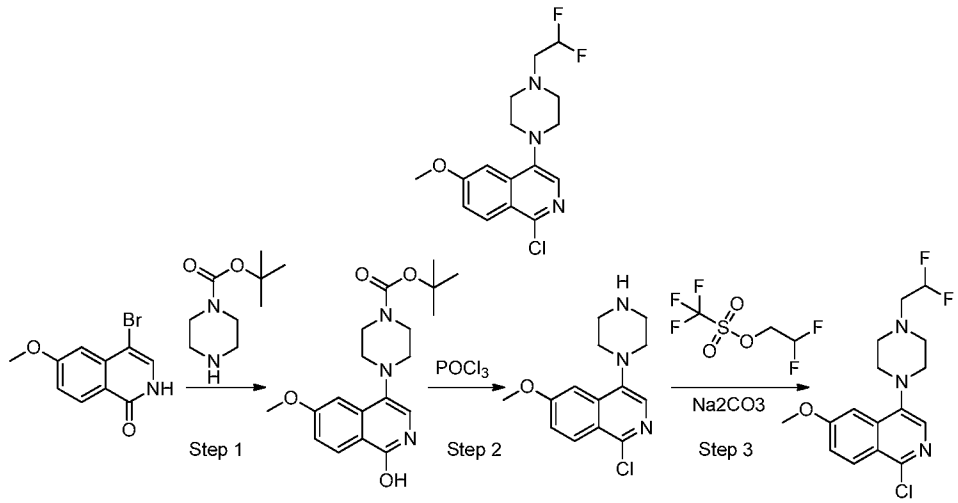
To a solution of 4-bromo-6-methoxyisoquinolin-1(2H)-one (0.2 g, 0.787 mmol) *and* (2S,6R)-2,6-dimethylmorpholine (0.181 g, 1.574 mmol) in ethylene glycol (2.5 ml) was added DIPEA (0.412 ml, 2.361 mmol). The reaction was irradiated in microwave at 145 °C for 1.5 h. The reaction mixture was adsorbed on silica was purified by silica gel chromatography (30% ethyl acetate in pet ether) to get desired compound (0.11 g, 48.5%) as solid. MS: MS *m/z* 289.18 (M^++1).

Step 2: Preparation of 4-(1-chloro-6-methoxyisoquinolin-4-yl)-2,6-dimethylmorpholine

A solution of 4-((2S, 6R)-2, 6-dimethylmorpholino)-6-methoxyisoquinolin-1(2H)-one (0.15 g, 0.520 mmol) in $POCl_3$ (5 ml) was refluxed for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (10% ethyl acetate in pet ether) to get the desired compound (0.085 g, 49%) as oil. MS: MS *m/z* 307.17 (M^++1).

Scheme: Preparation of 1-Chloro -4-(4-(2,2-difluoroethyl)piperazin-1-yl)isopropoxyphenyl)-6-methoxyisoquinoline & 1-Chloro -6-methoxy-4-(4-methylpiperazin-1-yl)isoquinoline:

Synthesis of 1-Chloro -4-(4-(2,2-difluoroethyl)piperazin-1-yl)isopropoxyphenyl)-6-methoxyisoquinoline:



Step 1: Preparation of tert-butyl 4-(1-hydroxy-6-methoxyisoquinolin-4-yl)piperazine-1-carboxylate

To a solution of 4-bromo-6-methoxyisoquinolin-1(2H)-one (0.5 g, 1.968 mmol) and tert-butyl piperizine-1-carboxylate (0.916 g, 4.92 mmol) in ethylene glycol (5 ml) was added DIPEA (1.0.31 ml, 5.90 mmol) and heated to 145 °C for overnight in sealed tube. The reaction mixture was diluted with water and extracted with ethyl acetate. Combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude compound (0.3 g, 29.4%). The crude compound was taken for the next step without further purification. MS: MS *m/z* 260.20 (M^++1).

Step 2: Preparation of 1-chloro-6-methoxy-4-(piperazin-1-yl)isoquinoline

A solution of tert-butyl 4-(1-hydroxy-6-methoxyisoquinolin-4-yl)piperazine-1-carboxylate (0.3 g, 1.157 mmol) in $POCl_3$ (5 ml) was refluxed for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (10% ethyl acetate in pet ether)

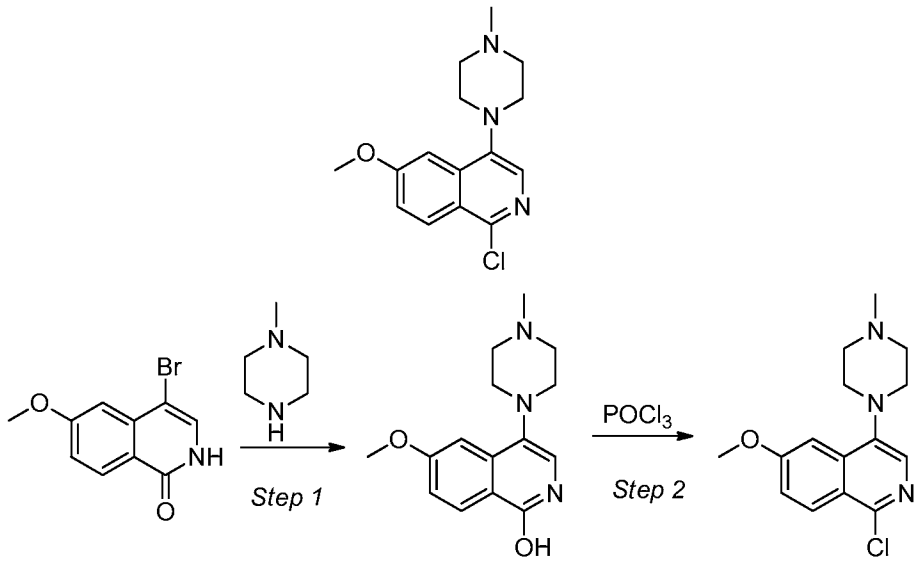
to get desired compound (0.2 g, 37.3%) as a gummy compound. MS: MS *m/z* 278.56 (M^++1).

Step 3: Preparation of 1-chloro-4-(4-(2,2-difluoroethyl)piperazin-1-yl)-6-methoxyisoquinoline

To a solution of 1-chloro-6-methoxy-4-(piperazin-1-yl)isoquinoline (0.2 g, 0.720 mmol) in DMF (5 ml) was added 2,2-Difluoroethyl trifluoromethanesulfonate (0.154 g, 0.720 mmol) followed by sodium carbonate (0.114 g, 1.080 mmol). The reaction mass was stirred until judged complete. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude compound. The crude compound was purified by silica gel chromatography (10% ethyl acetate in pet ether) to get desired compound (0.04 g, 15.93%) as semi solid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.18-8.15(d, *J* =12 Hz, 1H), 7.93 (s, 1H), 7.45-7.42 (d, *J* =12 Hz, 1H), 7.37(s, 1H), 6.36-5.76(tf, 1H), 3.97(s, 3H), 3.10(m, 4H), 2.84(m, 4H); ^{19}F NMR: δ ppm -118.59 (1 F); MS: MS *m/z* 342.19 (M^++1).

Scheme: Preparation of 1-Chloro-6-methoxy-4-(4-methylpiperazin-1-yl) isoquinoline:

Synthesis of 1-Chloro -6-methoxy-4-(4-methylpiperazin-1-yl)isoquinoline:



Step 1: Preparation of 6-methoxy-4-(4-methylpiperazin-1-yl) isoquinolin-1(2H)-one

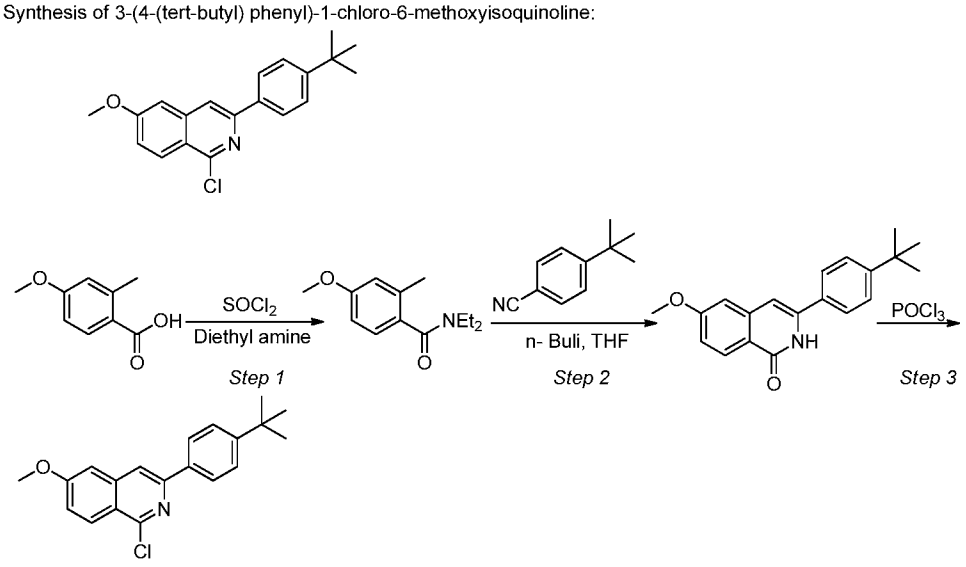
To a solution of 4-bromo-6-methoxyisoquinolin-1(2H)-one (0.25 g, 0.984 mmol) and 1-methylpiperazine (0.197 g, 1.968 mmol) in ethylene glycol (2 ml) was added DIPEA (0.516 ml, 2.95 mmol). The reaction was irradiated in microwave at 140 °C for 1 h. The reaction mixture was adsorbed on silica was purified by silica gel chromatography (30% ethyl acetate in pet ether) to get the desired compound (0.16 g, 53.5%) as solid. MS: MS *m/z* 274.18 (M^++1).

Step 2: Preparation of 1-chloro-6-methoxy-4-(4-methylpiperazin-1-yl)isoquinoline

A solution of 6-methoxy-4-(4-methylpiperazin-1-yl)isoquinolin-1(2H)-one (0.16 g, 0.585 mmol) in $POCl_3$ (5 ml) was refluxed for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (10% MeOH in $CHCl_3$) to get desired compound (0.05 g, 27.8%) as solid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.18-8.15(d, *J*=12 Hz, 1 H), 7.92 (s, 1 H), 7.45-7.42 (d, *J*=12 Hz, 1 H), 7.36(s, 1H), 3.97(s, 3H), 3.09(m, 4H), 2.52(m, 4H), 2.31(s, 3H); MS: MS *m/z* 292.15 (M^++1).

Scheme: Preparation of 3-(4-(tert-butyl)phenyl)-1-chloro-6-methoxyisoquinoline

Synthesis of 3-(4-(tert-butyl) phenyl)-1-chloro-6-methoxyisoquinoline:



Step 1: Preparation of N, N-diethyl-4-methoxy-2-methylbenzamide

4-methoxy-2-methylbenzoic acid (3.0 g, 18.05 mmol) was taken in thionyl chloride (20 ml) and refluxed for 1 h at 80 °C. The reaction mixture was evaporated under reduced pressure. Under nitrogen the crude was quenched with diethyl amine (1.870 ml, 18.05 mmol) slowly under cooling conditions. The reaction mixture was dissolved in water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get desired compound (2.3 g, 54.7%) as oil. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.06-7.04(d, *J* =8 Hz, 1H), 6.79 (s, 1 H), 6.78-6.76 (d, *J* =8 Hz, 1H), 3.75(s, 3H), 3.43(br, s, 2H), 3.06-3.05(m, 2H),2.16(s, 3H), 1.14(d, *J* =8 Hz, 3H), 0.95(d, *J* =8 Hz, 3H).

Step 2: Preparation of 3-(4-(tert-butyl)phenyl)-6-methoxyisoquinolin-1(2H)-one

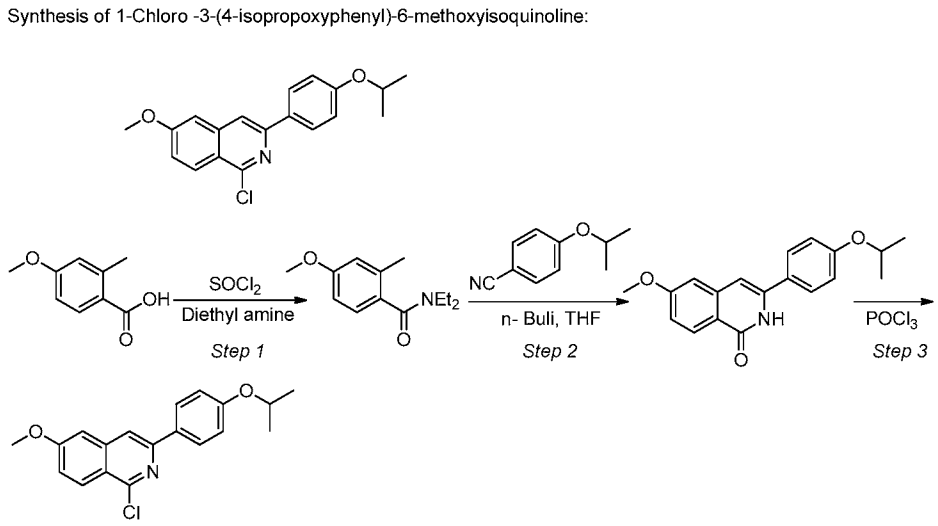
To a stirred solution of N,N-diethyl-4-methoxy-2-methylbenzamide (1g, 4.52 mmol) in THF (10 ml) was added n-BuLi (2.82 ml, 4.52 mmol, in hexane) at -78 °C and stirred for 1 h. Then to this 4-(tert-butyl)benzonitrile (0.72 g, 4.52 mmol) was added at same temperature and allowed to warm to room temperature and continued the stirring for another 1 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOac(2*100ml). The organic phase was washed with brine,dried on Na_2SO_4, and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get desired compound (0.72 g, 46.7%) as a solid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 11.26(s , 1H), 8.11-8.09(d, *J* =8 Hz, 1H), 7.73-7.71 (d, *J* =8 Hz, 2H), 7.52-7.50 (d, *J* =8 Hz, 2H), 7.06 (s, 1H), 7.05-7.03(d, *J* =8 Hz, 1 H), 6.82(s, 1H), 3.89(s,3H), 1.32(s, 9H); MS: MS *m/z* 308.2 (M^++1).

Step 3: Preparation of 3-(4-(tert-butyl)phenyl)-1-chloro-6-methoxyisoquinoline

A solution of 3-(4-(tert-butyl)phenyl)-6-methoxyisoquinolin-1(2H)-one (0.7 g, 2.277 mmol) in $POCl_3$ (7 ml) was refluxed for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica

gel chromatography (10% ethyl acetate in pet ether) to get desired compound (0.21 g, 28.0%) as solid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.34(s, 1 H), 8.18-8.16 (d, *J* =8 Hz, 1 H), 8.08-8.06(d, *J* =8 Hz, 2 H), 7.57-7.55 (d, *J* =8 Hz, 2 H), 7.41 (s, 1H), 7.40-7.38(d, *J* =8 Hz, 1 H), 3.97(s,3H), 1.34(s, 9H); MS: MS *m/z* 362.2 (M^++1).

Scheme: Preparation of 1-chloro-3-(4-isopropoxyphenyl)-6-methoxyisoquinoline



Step 1: Preparation of N, N-diethyl-4-methoxy-2-methylbenzamide

4-methoxy-2-methylbenzoic acid (3.0 g, 18.05 mmol) was taken in thionyl chloride (20 ml) and refluxed for 1 h at 80 °C. The reaction mixture was evaporated under reduced pressure. Under nitrogen the crude was quenched with diethyl amine (1.870 ml, 18.05 mmol) slowly under cooling condition. The reaction mixture was dissolved in water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get desired compound (2.3 g, 54.7%) as an oil.^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.06-7.04(d, *J* =8 Hz, 1 H), 6.79 (s, 1 H), 6.78-6.76 (d, *J* =8 Hz, 1H), 3.75(s, 3H), 3.43(br, s, 2H), 3.06-3.05(m, 2H),2.16(s,3H), 1.14(d, *J* =8 Hz, 3 H), 0.95(d, *J* =8 Hz, 3 H).

Step 2: Preparation of 3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1(2H)-one

To a stirred solution of N,N-diethyl-4-methoxy-2-methylbenzamide (3.5g, 15.82 mmol) in THF(35 ml) was added n-BuLi (2.82 ml, 4.52 mmol, in hexane) at -

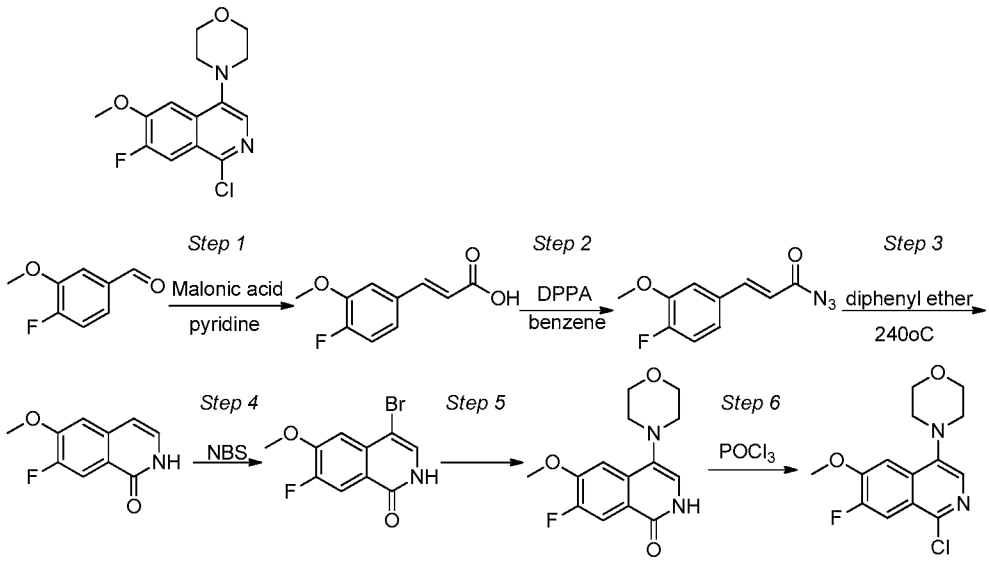
78 °C and stirred for 1 h. 4-isopropoxy benzonitrile (2.55 g, 15.82 mmol) was added at same temperature and allowed to warm to room temperature and continued the stirring for another 1 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc(2*100ml). The organic phase was washed with brine then dried on Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get desired compound (3.5 g, 71.5%) as white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 11.21(s , 1H), 8.09-8.07(d, *J* =8 Hz, 1 H), 7.71-7.69 (d, *J* =8 Hz, 2 H), 7.14 (d, *J* =8 Hz, 1 H), 7.03-7.01(d, *J* =8 Hz, 3 H), 6.76(s, 1H), 4.71(m, 1H), 3.88(s, 3H), 1.30(m, 6H); MS: MS *m/z* 310.7 (M^++1).

Step 3: Preparation of 1-chloro-3-(4-isopropoxyphenyl)-6-methoxyisoquinoline

A solution of 3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1(2H)-one (3.5 g, 11.31 mmol) in $POCl_3$ (11 ml) was refluxed for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (10% ethyl acetate in pet ether) to get desired compound (2.5 g, 67.4%) as pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.06-8.04 (d, *J* =8 Hz, 1H), 8.03-8.01(d, *J* =8 Hz, 2 H), 7.81 (s, 1H), 7.22-7.20(d, *J* =8 Hz, 1H), 7.00(s, 1H), 6.99-6.97(d, *J* =8 Hz, 1H), 4.63(m, 1H), 3.96(s,3H), 1.38(m, 6H).

Scheme: Preparation of 4-(1-Chloro-7-fluoro-6-methoxy isoquinoline-4-yl) morpholine

Synthesis of 4-(1-Chloro-7-fluoro-6-methoxy isoquinoline-4-yl) morpholine:



Step 1: Preparation of (E)-3-(4-fluoro-3-methoxyphenyl) acrylic acid

To a solution of 4-fluoro-3-methoxybenzaldehyde (30 g, 195 mmol) in pyridine (134 ml) and piperidine (4.12 ml) was added malonic acid (30.4 g, 292 mmol) at room temperature. The reaction mass was refluxed for 18 h. The solvent was evaporated under reduced pressure and the residue was acidified with 1.5N HCl solution. The precipitated solid was filtered washed with pet ether to get crude compound (37 g, 97%) as white solid. The crude compound was taken to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.37 (s, 1H), 7.59-7.55 (d, *J* = 16 Hz, 1H), 7.53 (s, 1H), 7.26-7.22 (m, 2H), 6.59-6.55 (d, *J* = 16 Hz, 1H), 3.89 (s, 3H); MS: MS *m/z* 195.0 (M^+-1).

Step 2: Preparation of (E)-3-(4-fluoro-3-methoxyphenyl) acryloyl azide

To a solution of (E)-3-(4-fluoro-3-methoxyphenyl)acrylic acid (25 g, 127 mmol) in benzene (250 ml) was added triethylamine (35.5 ml, 255 mmol) followed by DPPA (35.1 g, 127 mmol) at room temperature. The reaction mass was stirred at the same temperature for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude compound. The crude compound was purified by conventional column chromatography (Silica gel, 60-120 mesh) using 10% ethyl acetate in pet ether as

mobile phase to get the desire compound as white solid (15 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.70-7.66 (d, *J* = 16 Hz, 1H), 7.12-7.07 (m, 3H), 6.35-6.31 (d, *J* = 16 Hz, 1H), 3.92 (s, 3H).

Step 3: Preparation of 7-fluoro-6-methoxyisoquinolin-1(2H)-one

To a hot (125 °C) diphenyl ether (20 ml) was added (E)-3-(4-fluoro-3-methoxyphenyl)acryloyl azide (4 g, 18.08 mmol) portion wise. The reaction was heated at 250 °C for 4 h. The reaction mass was cooled to room temperature and diluted with pet ether. The precipitated solid was filtered washed with pet ether to get crude compound (3.1 g, 89%). The crude compound was taken to the next step without further purification. MS: MS *m/z* 194.1 (M^++1).

Step 4: Preparation of 4-bromo-7-fluoro-6-methoxyisoquinolin-1(2H)-one

To a solution of 7-fluoro-6-methoxyisoquinolin-1(2H)-one (1.5 g, 7.7 mmol) in acetonitrile (3 ml) was added NBS (1.382 g, 7.7 mmol) at room temperature under argon atmosphere. The reaction mass was stirred at the same temperature for 2 h. The reaction mass was cooled to room temperature and precipitated solid was filtered to get crude compound (1.25 g, 59.2%). The crude compound was taken to the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 11.59 (s, 1H), 7.93-7.91 (d, *J* =8 Hz, 1H), 7.56 (s, 1H), 7.29-7.27 (d, *J* =8 Hz, 1H), 4.03 (s, 3H); MS: MS *m/z* 272.03 (M^++2).

Step 5: Preparation of 7-fluoro-6-methoxy-4-morpholinoisoquinolin-1(2H)-one

To a solution of 4-bromo-7-fluoro-6-methoxyisoquinolin-1(2H)-one *(0.5 g,* 1.838 mmol*)* and morpholine (0.4 g, 4.59 mmol*)* in ethylene glycol (2.5 ml) was added DIPEA (1.031 ml, 5.90 mmol). The reaction was irradiated in microwave at 145 °C for 1.5 h. The reaction was cooled to ambient temperature and diluted with water. The aqueous layer was extracted with EtOAc. The organic layer was washed with 1N HCl, followed by washing with brine. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get the crude compound. The crude compound (0.25 g, 31.8%) was taken to the next step without further purification. MS: MS *m/z* 279.22 (M^++1).

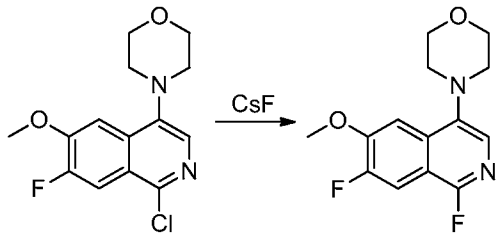
Step 6: Preparation of 4-(1-chloro-7-fluoro-6-methoxyisoquinolin-4-yl)morpholine

A solution of 7-fluoro-6-methoxy-4-morpholinoisoquinolin-1(2H)-one (0.25 g, 0.898 mmol) in $POCl_3$ (5 ml) was refluxed for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The

aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (30% ethyl acetate in pet ether) to get desired compound (0.13 g, 46.8%) as solid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.98-7.95(m, 2H), 7.56-7.54 (d, *J* =8 Hz, 1 H), 7.45-7.40 (m, 2H), 4.08(s, 3H), 3.89-3.86(m, 4H), 3.11-3.09(m, 4H); MS: MS *m/z* 297.07 (M^++1).

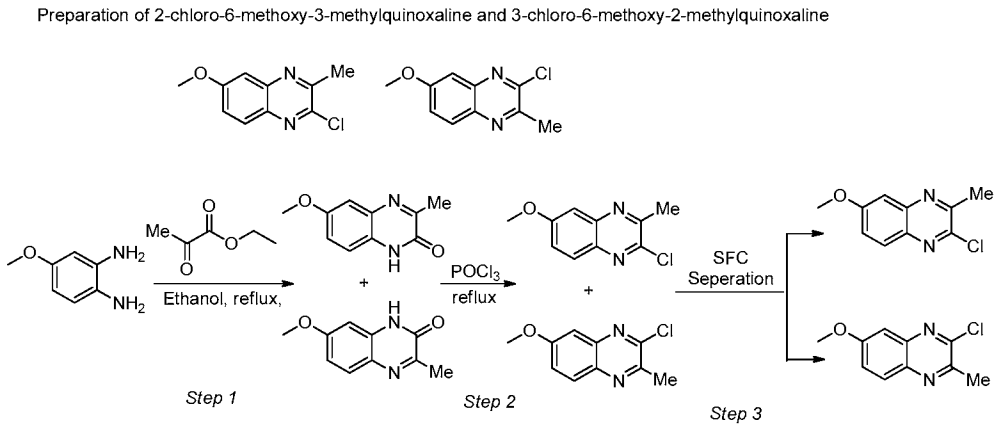
Scheme : Preparation of 4-(1, 7-difluoro-6-methoxyisoquinolin-4-yl) morpholine

Synthesis of 4-(1,7-difluoro-6-methoxyisoquinolin-4-yl)morpholine:



To a solution of 4-(1-chloro-7-fluoro-6-methoxyisoquinolin-4-yl)morpholine (0.12 g, 0.404 mmol) in DMSO(2 ml) was added cesium fluoride (0.245 g, 1.618 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 145 °C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get the desired compound (0.06 g, 51.9%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.94-7.91 (d, *J* = 12 Hz, 1H), 7.73 (s, 1H), 7.56-7.53 (d, *J* = 12 Hz, 1H), 4.07 (s, 3H), 3.88-3.86(m, 4H), 3.08-3.06(m, 4H); ^{19}F NMR: δ ppm -130.03 (1F), -76.45 (1F); MS: MS *m/z* 281.10 (M^++1).

Scheme: Preparation of 2-chloro-6-methoxy-3-methylquinoxaline and 3-chloro-6-methoxy-2-methylquinoxaline



Step 1: Preparation of 6-methoxy-3-methylquinoxalin-2(1H)-one and 7-methoxy-3-methylquinoxalin-2(1H)-one

To a solution of 4-methoxybenzene-1,2-diamine (1 g, 7.24 mmol) in ethanol(10 ml) was added ethyl 2-oxopropanoate (0.84 g, 7.24 mmol)). The reaction mass was heated at reflux for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate and then evaporated to dryness to get the crude compound. The crude compound was washed with pet ether to get the product (1.20 g, 6.31 mmol, 87 % yield) as a mixture of regioisomers (black solid). This crude compound was taken to the next step without separation of isomers.^{1}H NMR (400 MHz, DMSO-d6): δ ppm 12.20(br, s , 2H), 7.61-7.59(d, *J* =8 Hz, 1H), 7.22-7.20 (d, *J* =8 Hz, 2H), 7.19 (s, 1H), 7.14-7.12(d, *J* =8 Hz, 1H), 6.88-6.86(d, *J* =8 Hz, 1H), 6.74-6.72(d, *J* =8 Hz, 1H), 3.81(s,6H), 2.50(m, 3H), 2.37(m,3H); MS: MS *m/z 191.10* (M^{+}+1).

Step 2: Preparation of 2-chloro-6-methoxy-3-methylquinoxaline and 3-chloro-6-methoxy-2-methylquinoxaline

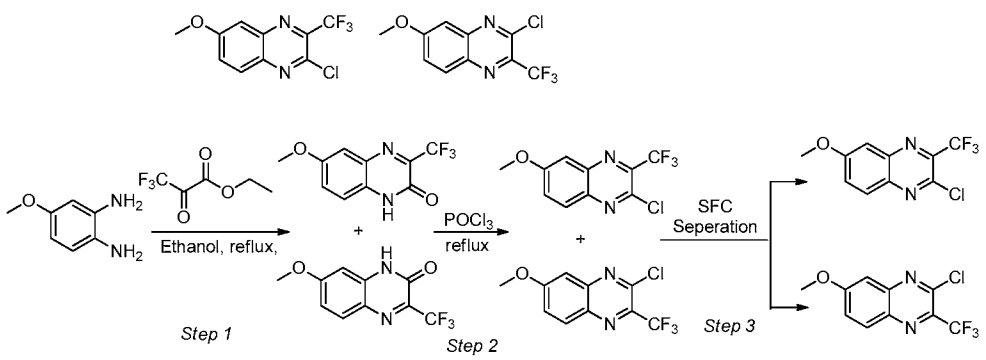
A solution of 6-methoxy-3-methylquinoxalin-2(1H)-one & 7-methoxy-3-methylquinoxalin-2(1H)-one (1.2 g, 6.31 mmol) in $POCl_3$ (10 ml) was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium

sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get regioisomers as a mixture. The mixture of regioisomers were separated by SFC purification to afford 2-chloro-6-methoxy-3-methylquinoxaline (0.51 g, 38.7%) and 3-chloro-6-methoxy-2-methylquinoxaline (required isomer) (0.48 g, 36.5%) as off white solids.

2-chloro-6-methoxy-3-methylquinoxaline: ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.92-7.90 (d, *J* = 8 Hz, 1H), 7.49-7.44 (m, 2H), 3.95 (s, 3H), 3.31 (s, 3H); MS: MS *m/z 209.14* (M^++1).

3-chloro-6-methoxy-2-methylquinoxaline: ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.97-7.95 (d, *J* = 8 Hz, 1H), 7.51-49 (d, *J* = 8 Hz, 1H), 7.40 (s, 1H), 3.94 (s, 3H), 2.72 (s, 3H); MS: MS *m/z 209.14* (M^++1).

Scheme: Preparation of 2-chloro-6-methoxy-3-(trifluoromethyl)quinoxaline and 3-chloro-6-methoxy-2-(trifluoromethyl)quinoxaline



Step 1: Preparation of 6-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one and 7-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one

To a solution of 4-methoxybenzene-1,2-diamine (1 g, 7.24 mmol) in ethanol(10 ml) was added ethyl 3,3,3-trifluoro-2-oxopropanoate (1.23 g, 7.24 mmol)). The reaction mass was heated at reflux for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate and then evaporated to dryness to get the crude compound. The crude compound was washed with pet ether to get the product (1.55 g, 88 % yield) as a mixture of regioisomers (black solid). This crude compound was taken to the next step without separation of

isomers. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 12.92(br, s, 2H), 7.84-7.81(d, *J* =12 Hz, 1H), 7.44-7.33 (m, 4H), 7.82 (s, 1H), 3.87(s, 6H), MS: MS *m/z 245.15* (M^++1).

Step 2: Preparation of 2-chloro-6-methoxy-3-(trifluoromethyl)quinoxaline and 3-chloro-6-methoxy-2-(trifluoromethyl)quinoxaline

A solution of 6-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one & 7-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one (0.90 g, 3.69 mmol) in $POCl_3$ (10 ml) was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The combine organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get regioisomers as mixture. The mixture of regioisomers were separated by SFC purification to afford 2-chloro-6-methoxy-3-methylquinoxaline (0.51 g, 38.7%) and 3-chloro-6-methoxy-2-methylquinoxaline (required isomer) (0.48 g, 36.5%) as off white solids.

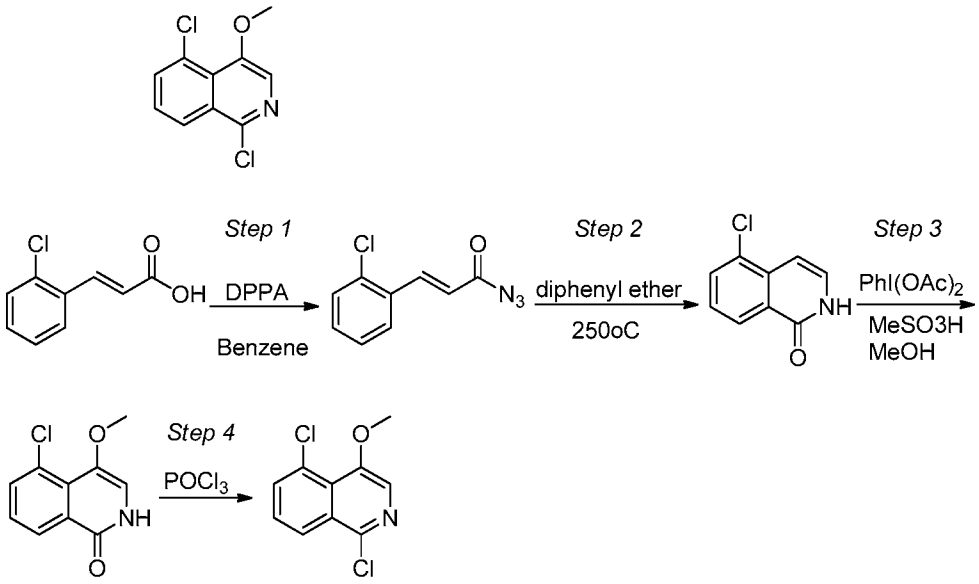
The mixture of regioisomers were separated by SFC purification to afford 2-chloro-6-methoxy-3-methylquinoxaline (required isomer) *(*0.31 g, 32%) and 3-chloro-6-methoxy-2-methylquinoxaline (0.15 g, 15.5%) as off white solids.

2-chloro-6-methoxy-3-(trifluoromethyl)quinoxaline: ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.10-8.07 (d, *J* = 12 Hz, 1H), 7.75-7.44 (m, 2H), 3.95 (s, 3H); ^{19}F NMR: δ ppm -65.36(1F) MS: MS *m/z 263.10* (M^++1).

3-chloro-6-methoxy-2-(trifluoromethyl)quinoxaline: ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.11-8.08 (d, *J* = 12 Hz, 1H), 7.78-7.75 (d, *J* = 12 Hz, 1H), 7.68 (s, 1H), 4.00 (s, 3H); ^{19}F NMR: δ ppm -65.36(1F) MS: MS *m/z 263.09* (M^++1).

Scheme: Preparation of 1,5-dichloro-4-methoxyisoquinoline

Synthesis of 1, 5-Dichloro-4-methoxyisoquinoline:



Step 1: Preparation of (E)-3-(2-chlorophenyl) acryloyl azide

To a solution of (E)-3-(2-chlorophenyl) acrylic acid (13 g, 71.2 mmol) in benzene (100 ml) was added triethylamine (14.4 g, 141 mmol) followed by DPPA (19.5 g, 71.2 mmol) at room temperature. The reaction mass was stirred at the same temperature for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude compound. The crude compound was purified by conventional column chromatography (Silica gel, 60-120 mesh) using 10% ethyl acetate in pet ether as mobile phase to get the desire compound as pale yellow solid (14 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.19-8.15 (d, J = 16 Hz, 1H), 7.63-7.61 (d, J = 8 Hz, 1H), 7.44-7.42 (m, 1H), 7.36-7.26 (m, 2H), 6.44-6.40 (d, J = 16 Hz, 1H).

Step 2: Preparation of 5-choroisoquinolin-1(2H)-one

To a hot (125°C) diphenyl ether (10 ml) was added (E)-3-(2-chlorophenyl) acryloyl azide (2 g, 9.63 mmol) portion wise. The reaction was heated at 250°C for 2 h. The reaction mass was cooled to room temperature and diluted with pet ether. The precipitated solid was filtered washed with pet ether to get crude compound (1.1 g,

63.6%) as yellow solid. The crude compound was taken to the next step without further purification. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.29-8.27 (d, *J* = 8 Hz, 1H), 7.84-7.82 (d, *J* = 8 Hz, 1H), 7.49 (t, *J* = 8 Hz, 1H), 7.32-7.30 (d, *J* = 8 Hz, 1H), 6.98-6.96 (d, *J* = 8 Hz, 1H); MS: MS *m/z* 180.7 (M^++1).

Step 3: Preparation of 5-chloro-4-methoxyisoquinolin-1-(2H)-one

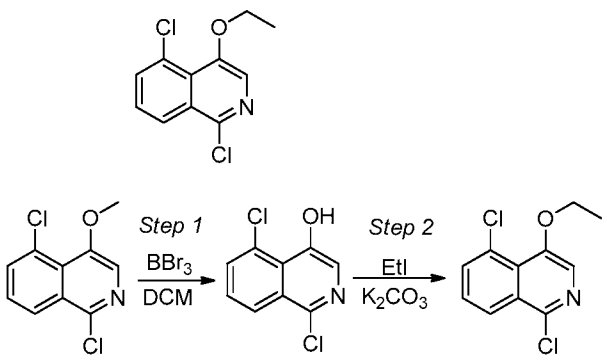
To a solution of 5-choroisoquinolin-1(2H)-one (3.8 g, 21.2 mmol) in methanol (70 ml) was added iodosobenzenediacetate (7.5 g, 23.4 mmol) followed by methane sulphonic acid (2.45 g, 25.5 mmol) at room temperature. The reaction mass was heated at reflux for 3 h. The solvent was evaporated and the residue was diluted with cold water. The precipitated solid was filtered, washed with water to get crude compound (3.9 g, 88%) as a light red colored solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.06-8.03 (d, *J* = 12 Hz, 1H), 7.60-7.57 (d, *J* = 12 Hz, 1H), 7.42 (d, *J* = 8 Hz, 1H), 7.01-6.99 (br s, 1H), 3.51 (s, 3H); MS: MS *m/z* 209.1 (M^++1).

Step 4: Preparation of 1,5-dichloro-4-methoxyisoquinoline

A solution of 5-chloro-4-methoxyisoquinolin-1-(2H)-one (6.4 g, 30.5 mmol) in $POCl_3$ (45 ml) was refluxed for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The precipitated solid was filtered, washed with water to get crude compound (4 g, 57.4%) as a light brown colored solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.28-8.25 (d, *J* = 12 Hz, 1H), 7.87 (s, 1H), 7.79-7.76 (d, *J* = 12 Hz, 1H), 7.58-7.54 (m, 1H), 4.03 (s, 3H); MS: MS *m/z* 228.0 (M^++1).

Scheme : Preparation of 1,5-dichloro-4-ethoxyisoquinoline

Synthesis of 1, 5-Dichloro-4-ethoxyisoquinoline:



Step 1: Preparation of 1,5-dichloro-4-hydroxyisoquinoline

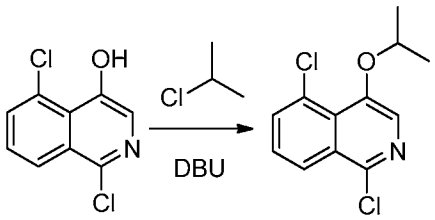
A solution of 1,5-dichloro-4-methoxyisoquinoline (1.2 g, 5.26 mmol) in DCM (15 ml) was added BBr_3 (9.23 g, 34.8 mmol) at 0°C drop wise. The reaction mass was refluxed for 5 h. The residue was cooled and quenched with methanol. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The precipitated solid was filtered, washed with water to get crude compound (0.7 g, 62.2%) as light brown color solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.28-8.25 (d, *J* = 12 Hz, 1H), 7.85-7.82 (m, 2H), 7.68-7.64 (m, 1H); MS: MS *m/z* 214.0 (M^++1).

Step 2: Preparation of 1,5-dichloro-4-ethoxyisoquinoline

To a solution of 1,5-dichloroisoquinolin-4-ol (0.5 g, 2.33 mmol) in acetonitrile (15 ml) was added K_2CO_3 (0.96 g, 7.01 mmol) followed by ethyl iodide (0.72 g, 4.67 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get 1,5-dichloro-4-ethoxyisoquinoline (0.3 g, 53%) as pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.26-8.24 (d, *J* = 8Hz, 1H), 7.86 (s, 1H), 7.78-7.76 (d, *J* = 8Hz, 1H), 7.55 (t, *J* = 8Hz, 1H), 4.26-4.21 (m, 2H), 1.57 (t, *J* = 7 Hz, 3H); MS: MS *m/z* 242.6 (M^++1).

Scheme: Preparation of 1,5-dichloro-4-isopropoxyisoquinoline

Synthesis of 1, 5-Dichloro-4-isopropoxyisoquinoline:



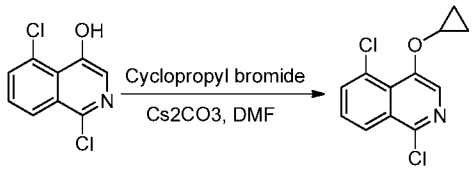
To a solution of 1,5-dichloroisoquinoline-4-ol (0.5 g, 2.33 mmol) in DBU (1.06 g, 7.01 mmol) was added isopropyl chloride (0.27 g, 3.5 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 120°C for

6 h. The reaction mass was quenched with 1.5 N HCl solution and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (0.3 g, 50.1%) as pale yellow solid.

^{1}H NMR (400 MHz, DMSO): δ ppm 8.26-8.23 (d, *J* = 12 Hz, 1H), 8.11 (s, 1H), 7.96-7.94 (d, *J* = 8 Hz, 1H), 7.76 (t, *J* = 8 Hz, 1H), 4.93-4.90 (m, 1H), 1.42-1.40 (d, *J* = 8 Hz, 6H); MS: MS *m/z* 256.7 (M^++1).

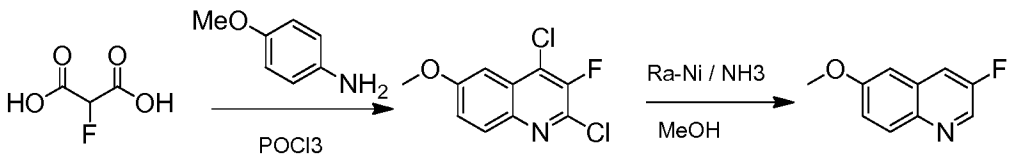
Scheme: Preparation of 1,5-dichloro-4- cyclopropoxyisoquinoline

Synthesis of 1, 5-Dichloro-4-cyclopropoxyisoquinoline:



To a solution of 1,5-dichloroisoquinolin-4-ol (0.5 g, 2.33 mmol) in DBU (1.7 ml, 11.68 mmol) was added cyclopropylbromide (0.93 ml, 11.68 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 120°C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (0.01 g, 2.1%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.27-8.24 (m, 2H), 7.76-7.74 (d, *J* = 8 Hz, 1H), 7.54 (t, *J* = 8 Hz, 1H), 3.96-3.94 (m, 1H), 0.95-0.90 (m, 4H).

Scheme: Synthesis of 3-Fluoro-6-methoxyisoquinoline:



Step: 1 Synthesis of 2, 4-dichloro-3-fluoro-6-methoxyquinoline:

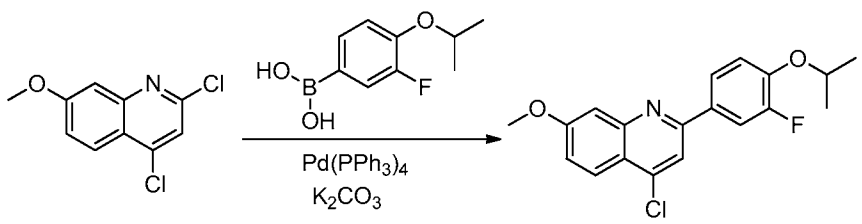
2-fluoromalonic acid (.67 g, 5.49 mmol) was combined with $POCl_3$ (4.5 ml, 48.3 mmol) and heated to 80 °C to dissolve all of the solids. Once the solids were dissolved, the reaction was cooled to 60 °C; 4-methoxyaniline (0.676 g, 5.49 mmol) was added portion wise carefully. Once the addition was complete, the reaction mixture was slowly heated and refluxed at 100-105 °C for 2h.

The volatiles were removed under vacuumand the resulting residue was cooled to 0-10 °C; ice was carefully added into the reaction mixture, stirred vigorously to get the solid. NH_4OH is slowly added until the pH 9.5, stirred the resulting yellow suspension for another 10 min. Filtered the solids , washed with water dried the yellow solids to afford 2,4-dichloro-3-fluoro-6-methoxyquinoline (0.95 g, 3.86 mmol, 70.3 % yield). ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.93 (d, J = 9.1 Hz, 1H), 7.40-7.34 (dd, J = 9.0 Hz, J= 2.9 Hz, 1H), 7.26-7.25 (d, J= 2.9 Hz 1 H), 3.98 (s, 3H), MS: MS m/z 247.0 (M^++1).

Step 2: Synthesis of 3-Fluoro-6-methoxy quinoline

To a suspension of 2, 4-dichloro-3-fluoro-6-methoxyquinoline (0.9 g, 3.66 mmol) in ammonia in methanol (10 mL, 462 mmol) was added carefully the slurry of Raney Nickel (5 g, 3.66 mmol) in Methanol (10 mL). The resulting reaction mixture was hydrogenated at 150 psi pressure, stirred at room temperature for 24 h. Filtered the catalyst, washed with methanol, evaporated the filtrate under reduced pressure to afford crude mass, purified by silica gel chromatography eluting with 10% -50% ethyl acetate in pet-ether to afford 3-Fluoro-6-methoxy quinoline (0.27g, 41%) as pink solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 8.65 (d, J= 2.9Hz, 1H), 8.01-7.98 (d, J = 9 Hz, 1H) 7.67-7.64 (dd, J = 9 Hz, J= 2.9 Hz 1H), 7.33-7.30 (dd, J = 9.0 Hz, J= 2.9 Hz, 1H), 7.03 (d, J= 2.9 Hz 1H), 3.93 (s, 3H).

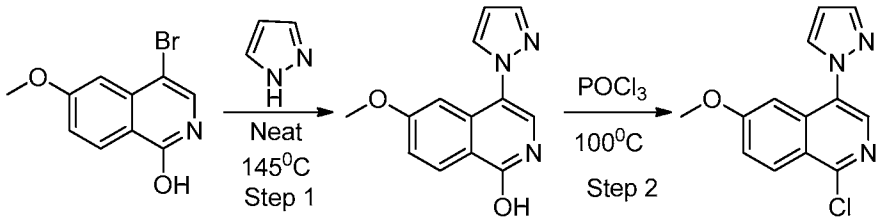
Synthesis of 4-chloro-2-(3-fluoro-4-isopropoxyphenyl)-7-methoxyquinoline



Step 1: Preparation of 4-chloro-2-(3-fluoro-4-isopropoxyphenyl)-7-methoxyisoquinoline

To a solution of 2,4-dichloro-7-methoxyisoquinolin (0.25 g, 1.1 mmol), 3-Fluoro-4-isopropoxyphenylboronicacid (0.21 g, 1.1 mmol) in 1,4-Dioxane (5 ml) and water (1 ml) was added K_2CO_3 (0.3 g, 2.2 mmol). The reaction mass was degasified for 20 min. Pd $(Ph_3P)_4$ (0.06 g, 0.05 mmol) was added to the above reaction mass and degasified again for 5 min at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 90°C for 18 h. The reaction mass was evaporated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (0.2 g, 54%) as white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) : δ ppm 8.08 (d, *J*=9.26 Hz, 1 H) 7.93 (dd, *J*=12.51, 2.25 Hz, 1 H) 7.80 (dt, *J*=8.50, 1.00 Hz, 1 H) 7.74 (s, 1 H) 7.45 (d, *J*=2.50 Hz, 1 H) 7.09 (t, *J*=8.50 Hz, 1 H), 3.99 (s, 3 H), 3.95 (m, 1 H), 1.41 (d, *J*=6.25 Hz, 6 H).

Scheme: Synthesis of 1-chloro-6-methoxy-4-(1H-pyrazol-1-yl) isoquinoline:



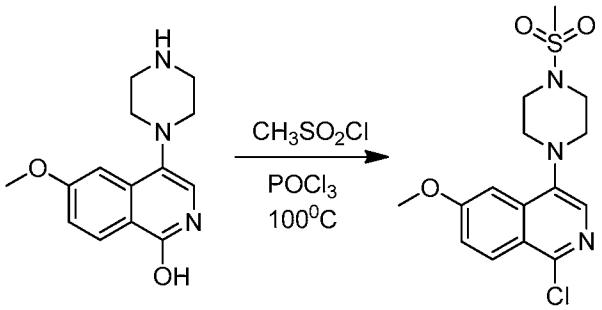
Step 1: Synthesis of (6-methoxy-4-(1H-pyrazol-1-yl) isoquinolin-1-ol

1H-pyrazole (0.201 g, 2.95 mmol) was taken in sealed tube vessel and heated to 80°C. To the melted compound 4-bromo-6-methoxyisoquinolin-1-ol (0.25 g, 0.984 mmol) was added and heating was raised to 150 °C and stirred for overnight. The reaction mixture was cooled to RT. The resulting solid (6-methoxy-4-(1H-pyrazol-1-yl) isoquinolin-1-ol (0.25 g, 0.114 mmol) 11.59 % yield) was taken to the next step without further purification. MS: MS *m/z* 242.10 (M^++1).

Step 2: Synthesis of 1-chloro-6-methoxy-4-(1H-pyrazol-1-yl) isoquinoline:

6-methoxy-4-(1H-pyrazol-1-yl) isoquinolin-1(2H)-one (0.25 g, 1.036 mmol) was taken in phosphorous oxychloride (5 mL) and stirred for 1 h at 100 °C. The volatiles were evaporated and the crude was poured into ice. The pH was adjusted to 9.0, extracted with ethyl acetate and washed with brine solution. The organic layer was dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure. The crude product was purified by silica gel chromatrography using 10% Ethyl acetate in Pet-ether to get 1-chloro-6-methoxy-4-(1H-pyrazol-1-yl) isoquinoline (0.019 g, 0.062 mmol, 6.00 % yield) as solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.77 - 8.84 (m, 2 H) 8.74 - 8.84 (m, 1 H) 8.52 - 8.58 (m, 2 H) 8.52 - 8.57 (m, 1 H) 8.28 - 8.34 (m, 1 H) 8.27 - 8.34 (m, 2 H) 7.90 - 7.96 (m, 1 H) 7.77 - 7.83 (m, 1 H) 7.46 - 7.52 (m, 1 H) 7.32 - 7.38 (m, 1 H) 6.58 - 6.66 (m, 1 H) 3.96 (s, 3 H). MS: MS *m/z* 260.10 (M^++1).

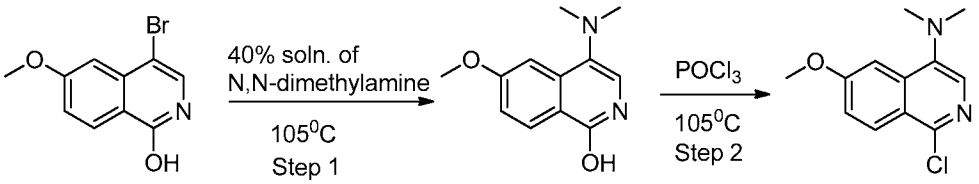
Synthesis of 1-chloro-6-methoxy-4-(4-(methylsulfonyl) piperazin-1-yl) isoquinoline:



6-methoxy-4-(piperazin-1-yl)isoquinolin-1-ol (0.15 g, 0.578 mmol) was taken in methane sulfonyl chloride (0.090 mL, 1.157 mmol) and added phosphorous oxychloride (5 mL) and stirred for 1 h at 110 °C. The volatiles were evaporated and the crude was poured into ice. This solution PH was adjusted to 9.0 and extracted with ethyl acetate andwashed with brine solution. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude sample was purified by silica gel chromatography using 45% ethyl acetate in pet ether to get 1-chloro-6-methoxy-4-(4-(methylsulfonyl)piperazin-1-yl)isoquinoline (0.041 g, 0.114 mmol, 19.72 % yield) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): ppm 8.18 (d, *J*=9.16 Hz, 1

H) 7.98 (s, 1 H) 7.42 - 7.50 (m, 1 H) 7.38 (s, 1 H), 3.99 (s, 3 H), 3.41 (br. s., 4 H) 3.19 (br. s., 4 H) 3.00 (s, 3 H). MS: MS *m/z* 346.20 (M^++1).

Synthesis of 1-chloro-6-methoxy-N, N-dimethylisoquinolin-4-amine



Step 1: Synthesis of 4-(Dimethylamine)-6-methoxyisoquinolin-1-ol

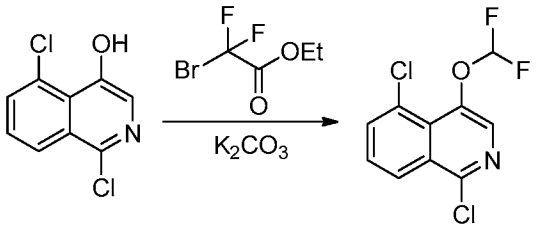
A solution of 4-bromo-6-methoxyisoquinolin-1(2H)-one (1 g, 3.94 mmol) in dimethylamine (5 ml, 39.5 mmol) was heated to 105°C for 48 h. After cooling, the reaction mixture was concentrated under reduced pressure to get 4-(Dimethylamino)-6-methoxyisoquinolin-1(2H)-one (0.8 g, 4.58 mmol, 85 % yield). MS: MS *m/z* 219.20 (M^++1).

Step 2: Synthesis of 1-chloro-6-methoxy-N, N-dimethylisoquinolin-4-amine.

To 4-(Dimethylamino)-6-methoxyisoquinolin-1(2H)-one (0.5 g, 2.291 mmol) was added $POCl_3$ (3 ml, 32.2 mmol) at room temperature. Then the reaction mixture was heated to 100°C for 1h.

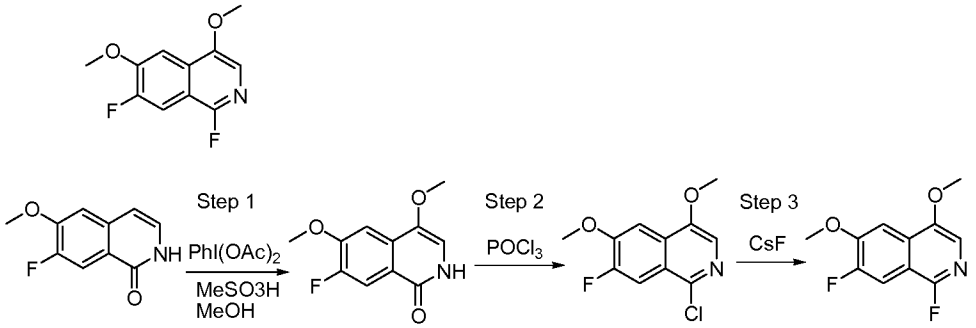
The reaction mixture was concentrated under reduced pressure; the resultant residue was suspended in 10% sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate, filtered, concentrated to afford the crude product. The crude was purified by silica gel chromatography eluting with 20% ethyl acetate in pet-ether to afford 1-chloro-6-methoxy-N,N-dimethylisoquinolin-4-amine (0.32 g, 1.352 mmol, 59.0 % yield). ^{1}H NMR (400 MHz, CHLOROFORM-*d*): ppm 8.20 (d, *J*=9.29 Hz, 1 H) 7.88 (s, 1 H) 7.42 (d, *J*=2.51 Hz, 1 H) 7.28 (d, *J*=2.51 Hz, 1 H) 3.99 (s, 3 H) 2.90 (s, 6 H) MS: MS *m/z* 237.20 (M^++1).

Synthesis of 1, 5-Dichloro-4-(difluoromethoxy) isoquinoline:



To a stirred solution of 1,5-dichloroisoquinolin-4-ol (0.3 g, 1.402 mmol) in DMF (10 mL) was added potassium carbonate (0.291 g, 2.102 mmol) followed by ethyl bromodifluoro acetate (0.216 mL, 1.682 mmol) under nitrogen at rt and was stirred for 30 min at the same temperature. Then temperature was raised to 120 °C and refluxed for 2 h. The reaction mixture was cooled to RT and poured into water, extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford crude product, purified by silica gel chromatography using 5% ethyl acetate in pet-ether to get pure 1,5-dichloro-4-(difluoromethoxy)isoquinoline (0.05 g, 0.182 mmol, 12.97 % yield) as pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): ppm 8.40-8.38 (d, J=8.0, 1H), 8.37 (s, 1H), 8.14-8.12(d, J=8.0, 1H), 7.90-7.88(t, J= 8.0, 1H), 7.55-7.18 (t, 1H) MS: MS *m/z* 265.20 (M^++1).

Synthesis of 1,7-Difluoro-4, 6-dimethoxyisoquinoline:



Step 1: Preparation of 7-fluoro-4,6-dimethoxyisoquinolin-1(2H)-one

To a solution of 7-fluoro-6-methoxyisoquinolin-1(2H)-one (6.3 g, 32.6 mmol) in methanol (70 ml) was added iodozobenzenediacetate (10.5 g, 32.6 mmol) followed by methane sulphonic acid (3.76 g, 39.1 mmol) at room temperature. The reaction

mass was heated at reflux for 3 h. The solvent was evaporated and the residue was diluted with cold water. The precipitated solid was filtered, washed with water to get crude compound (6.6 g, 91%) as a light red colored solid. MS: MS *m/z* 224.0 (M^++1).

Step 2: Preparation of 1-chloro-7-fluoro-4,6-dimethoxyisoquinoline

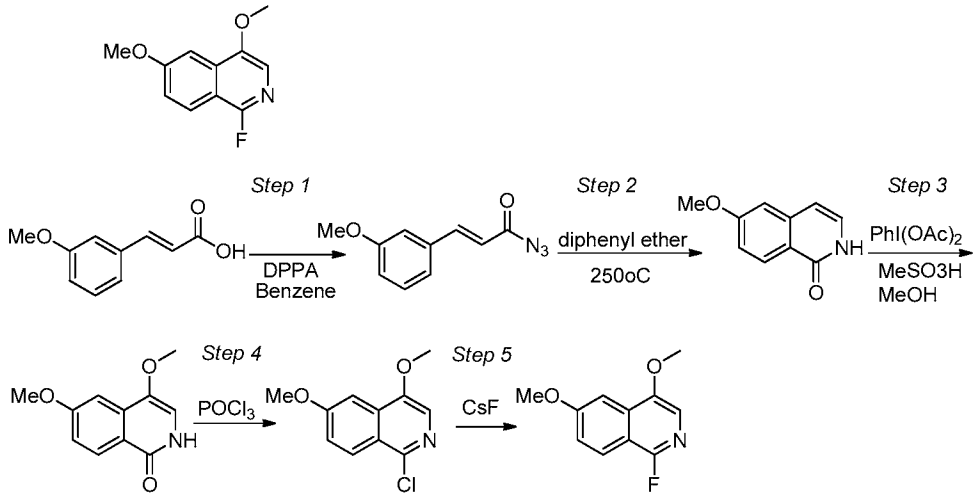
A solution of 7-fluoro-4, 6-dimethoxyisoquinolin-1(2H)-one (7.6 g, 34.1 mmol) in $POCl_3$ (50 ml) was refluxed for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get desired compound (2 g, 24.3%) as pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.88-7.85 (d, *J* = 12 Hz, 1H), 7.75 (s, 1H), 7.54-7.52 (d, *J* =8 Hz, 1 H), 4.05 (s, 3H); MS: MS *m/z* 242.0 (M^++1).

Step 3: Preparation of 1,7-difluoro-4,6-dimethoxyisoquinoline

To a solution of 1-chloro-7-fluoro-4,6-dimethoxyisoquinoline (2 g, 8.28 mmol) in DMSO (5 ml) was added cesium fluoride (2.51 g, 16.55 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 145°C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (475 mg, 25.5%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.69-7.67 (d, *J* = 8 Hz, 1H), 7.53-7.51 (d, *J* = 8 Hz, 1H), 7.45-7.44 (m, 1H), 4.05 (s, 3H), 4.03 (s, 3H); ^{19}F NMR: δ ppm -129.58 (1 F), -79.2 (1F); MS: MS *m/z* 226.0 (M^++1).

Scheme: Preparation of 1-fluoro-4,6-dimethoxyisoquinoline

Synthesis of 1-Fluoro-4, 6-dimethoxyisoquinoline:



Step 1: Preparation of (E)-3-(3-methoxyphenyl) acrylic azide

To a solution of (E)-3-(3-methoxyphenyl) acrylic acid (20 g, 112 mmol) in benzene (200 ml) was added triethylamine (22.72 g, 224 mmol) followed by DPPA (30.9 g, 112 mmol) at room temperature. The reaction mass was stirred at the same temperature for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with dichloromethane. Combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude compound. The crude compound was purified by conventional column chromatography (Silica gel, 60-120 mesh) using 10% ethyl acetate in pet ether as mobile phase to get the desire compound as white solid (18 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.73-7.69 (d, J = 16 Hz, 1H), 7.33-7.29 (t, J = 8 Hz, 1H), 7.26 (s, 1H), 7.14-7.12 (d, J = 8 Hz, 1H), 7.05 (s, 1H) 6.98-6.96 (d, J = 4 Hz, 1H), 6.43-6.39 (d, J = 16 Hz, 1H), 3.86 (s, 3H);

Step 2: Preparation of -6-methoxyisoquinolin-1(2H)-one

To a solution of (E)-3-(3-methoxyphenyl) acryloyl azide (7 g, 34.4 mmol) in 1,2-dichlorobenzene (70 ml) was added mercuric acetate (0.11 g, 0.34 mmol). The reaction was heated at 150 °C for 10 min and the temperature was raised to 180°C for 1 h. The reaction mass was cooled to room temperature and diluted with pet ether. The precipitated solid was filtered washed with pet ether to get crude compound (3.5 g, 58%) as yellow solid. The crude compound was taken to the next step without

further purification. ^{1}H NMR (400 MHz, DMSO): δ ppm 8.09-8.06 (d, *J* = 12 Hz, 1H), 7.14-7.11 (m, 2H), 7.05-7.03 (d, *J* = 8 Hz, 1 H), 6.48-6.46 (d, *J* = 4 Hz, 1 H), 3.86 (s, 3H); MS: MS *m/z* 176.0 (M^++1).

Step 3: Preparation of 4,6-dimethoxyisoquinolin-1(2H)-one

To a solution of 7-fluoro-6-methoxyisoquinolin-1(2H)-one (7 g, 40.0 mmol) in methanol (70 ml) was added iodozobenzenediacetate (14.16 g, 40.0 mmol) followed by methane sulphonic acid (11.52 g, 120 mmol) at room temperature. The reaction mass was heated at reflux for 3 h. The solvent was evaporated and the residue was diluted with cold water. The precipitated solid was filtered, washed with water to get crude compound (4 g, 48.8%) as a light red colored solid. ^{1}H NMR (400 MHz, DMSO): δ ppm 8.11-8.09 (d, *J* = 8 Hz, 1H), 7.19 (s, 1H), 7.13-7.11 (d, *J* = 8 Hz, 1 H), 6.72-6.71 (d, *J* = 12 Hz, 1 H), 3.89 (s, 3H), 3.79 (s, 3H); MS: MS *m/z* 206.1 (M^++1).

Step 4: Preparation of 1-chloro-4,6-dimethoxyisoquinoline

A solution of 4,6-dimethoxyisoquinolin-1(2H)-one (4 g, 19.49 mmol) in $POCl_3$ (40 mL) was refluxed for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get desired compound (1.2 g, 27.5%) as pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.16-8.13 (d, *J* = 12 Hz, 1H), 7.74 (s, 1H), 7.44-7.43 (d, *J* = 4 Hz, 1 H), 7.30-7.27 (d, *J* = 12 Hz, 1 H), 7.26 (s, 1H), 4.05 (s, 3H), 3.97 (s, 3H); MS: MS *m/z* 224.2 (M^++1).

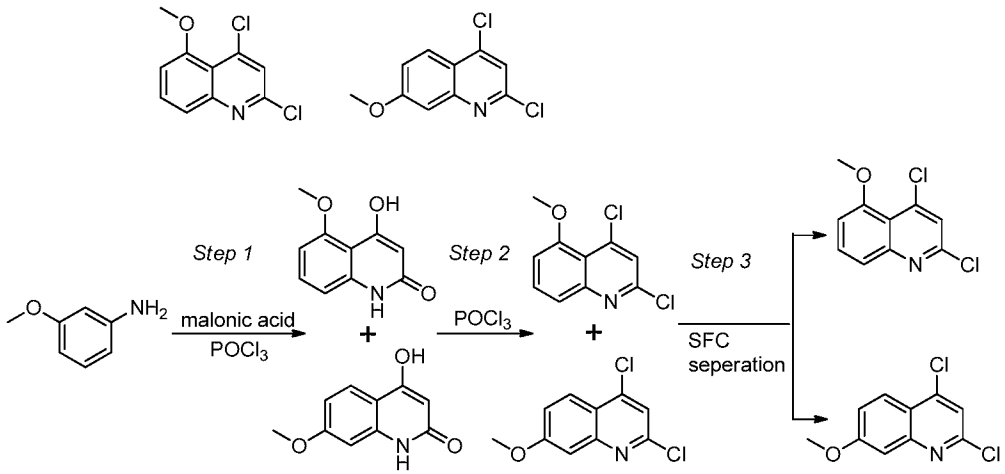
Step 5: Preparation of 1-fluoro-4,6-dimethoxyisoquinoline

To a solution of 1-chloro-4,6-dimethoxyisoquinoline (1.5 g, 6.71 mmol) in DMSO (15 ml) was added cesium fluoride (4 g, 26.8 mmol) at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 145°C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (280 mg, 20.15%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$):

δ ppm 7.99-7.97 (d, *J* = 8 Hz, 1H), 7.44-7.39 (m, 2H), 7.27-7.11 (m, 1H), 4.03 (s, 3H), 3.97 (s, 3H); ^{19}F NMR: δ ppm -79.32 (1F); MS: MS *m/z* 208.0 (M^++1).

Scheme: Preparation of 2,4-dichloro-5-methoxyquinoline & 2,4-dichloro-7-methoxyquinoline

Synthesis of 2, 4-Dichloro -5-methoxy quinoline & 2, 4-Dichloro -7-methoxy quinoline:



Step1: Preparation of 4-hydroxy-5-methoxyquinoline-2(1H)-one & 4-hydroxy-7-methoxyquinoline-2(1H)-one

$POCl_3$ (4.16 ml, 44.7 mmol) was added to the mixture of 3-methoxy aniline (5.0 g, 40.6 mmol) and malonic acid (4.22 g, 40.6 mmol). The reaction mass was heated to 105°C for 1 h. The reaction mass was diluted with water (20ml) and stirred for 30 min. The precipitated solid was filtered and washed with water. 2N NaOH solution (30 ml) was added to the solid and stirred for 18 hr. The remaining solid was filtered off and ethanol (5 ml) was added to the filtrate was acidified to PH 2 using conc. HCl. The precipitated solid was filtered and washed with water. The solid was dried under reduced pressure to get desired regio isomer in the ratio 50:50 (3 g, 38.6%) as white solid. ^{1}H NMR (400 MHz, DMSO): δ ppm 11.27-11.07 (m, 3H), 10.01 (s, 1H), 7.68-7.65 (d, J = 12 Hz, 1H), 7.41 (t, J = 12 Hz, 1H) 6.91-6.88 (d, J = 12 Hz, 1H), 6.76-6.72 (m, 3H), 5.62-5.60 (d, J = 8 Hz, 2H), 3.92 (s, 3H), 3.72 (s, 3H).

Step 2: Preparation of 2,4-dichloro-5-methoxyquinoline & 2,4-dichloro-7-methoxyquinoline

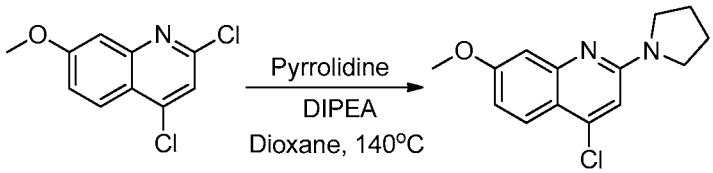
A solution of 4-hydroxy-5-methoxyquinoline-2(1H)-one & 4-hydroxy-7-methoxyquinoline-2(1H)-one (3 g, 15.70 mmol) in $POCl_3$ (3.66 ml, 39.2 mmol) was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to afford mixture of regioisomers.

This mixture of regioisomers was separated by SFC purification to afford 2, 4-dichloro-5-methoxyquinoline (0.7 g, 39%) and 2,4-dichloro-7-methoxyquinoline(required isomer) (1.3 g, 72.6%) as white solid.

2,4-dichloro-7-methoxyquinoline: ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.07-8.04 (d, *J* = 12 Hz, 1H), 7.35-7.34 (m, 2H), 7.28-7.26 (m, 1H), 3.94 (s, 3H);

2,4-dichloro-5-methoxyquinoline: ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.66-7.60 (m, 2H), 7.40 (m, 1H), 7.25 (s, 1H), 6.95-6.93 (d, *J* = 8 Hz, 1H), 3.97 (s, 3H).

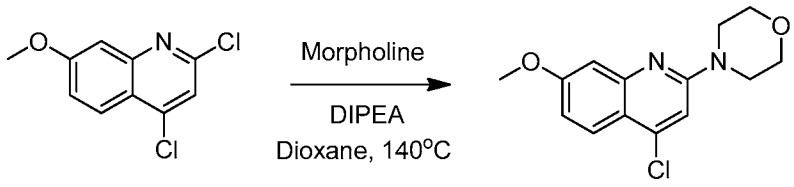
Scheme 17: Preparation of 4-Chloro-7-methoxy-2-(pyrrolidin-1-yl) quinoline



To a solution of 2,4-dichloro-7-methoxyquinoline (0.1 g, 0.43 mmol) in 1,4-Dioxane (10 ml) was added pyrrolidine (0.3 g, 0.43 mmol) fallowed by DIPEA (0.11 g, 0.87 mmol) at room temperature. The reaction mass was heated at 140°C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (50 mg, 43.4%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.86-7.83 (d, *J* = 12 Hz, 1H), 7.06 (s,1H), 6.88-6.85 (d, *J*

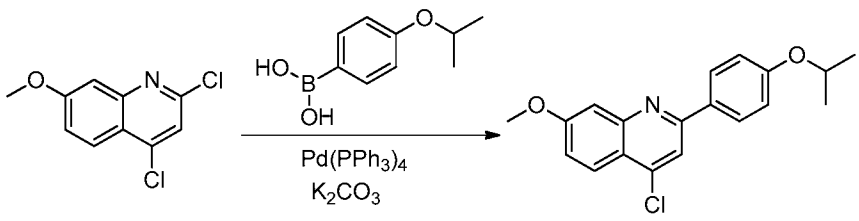
= 12 Hz, 1H), 6.67 (s, 1H), 3.91 (s, 3H), 3.58 (t, *J* = 8 Hz, 4H), 2.03 (t, *J* = 6 Hz, 1H); MS: MS *m/z* 263.1 (M^++1).

Scheme 18: Preparation of 4-(4-Chloro-7-methoxy quinoline-2-yl) morpholine



To a solution of 2,4-dichloro-7-methoxyquinoline (1 g, 4.38 mmol) in 1,4-dioxane (15 ml) was added morpholine (1.9 g, 4.38 mmol) fallowed by DIPEA (1.7 g, 13.15 mmol) at room temperature. The reaction mass was heated at 140°C for 18 h. The reaction mass was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (0.6 g, 49.1%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.89-7.86 (d, *J* = 12 Hz, 1H), 7.07 (s, 1H), 6.97-6.94 (d, *J* = 12 Hz, 1H), 6.89 (s, 1H), 3.91 (s, 3H), 3.85-3.82 (m, 4H), 3.69-3.66 (m, 4H); MS: MS *m/z* 279.1 (M^++1).

Scheme : Preparation of 1,7-difluoro-4-cyclopropoxyisoquinoline

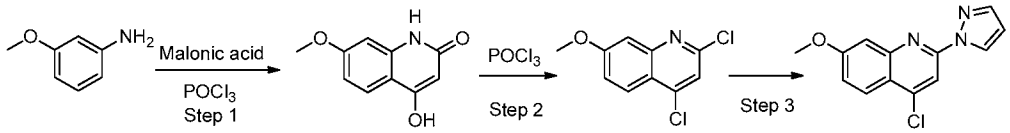


Step 1: Preparation of 4-chloro-2-(4-isopropoxyphenyl)-7-methoxyisoquinoline

To a solution of 2,4-dichloro-7-methoxyisoquinolin (0.7 g, 3.07 mmol), 4-isopropoxyphenylboronicacid (0.60 g, 3.38 mmol) in 1,4-Dioxane (15 ml) and water (10 ml) was added K_2CO_3 (0.84 g, 6.14 mmol). The reaction mass was degasified for 20 min. Pd $(Ph_3P)_4$ (0.17 g, 0.15 mmol) was added to the above reaction mass and

degasified again for 5 min at room temperature. The reaction vessel (Pressure tube) was sealed and heated at 90°C for 18 h. The reaction mass was evaporated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to get desired compound (0.85 g, 84%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.25-8.22 (d, *J* = 8 Hz, 1H), 8.13 (s, 1H), 8.07-8.05 (d, *J* = 8 Hz, 1H), 7.48-7.47 (d, *J* = 4 Hz, 1H), 7.34-7.32 (d , *J* = 8 Hz, 1H), 7.07-7.05 (m, 2H), 4.77-4.71 (m, 1H), 4.15 (s, 3H), 1.32-1.31 (d, J = 4 Hz, 6H); MS: MS *m/z* 328.20 (M^++1).

Scheme : Preparation 4-Chloro-7-methoxy-2-(1H-pyrazol-1-yl) quinoline



Step 1: Preparation of 4-hydroxy-5-methoxyquinoline-2(1H)-one & 4-hydroxy-7-methoxyquinoline-2(1H)-one

$POCl_3$ (4.16 ml, 44.7 mmol) was added to the mixture of 3-methoxy aniline (5.0 g, 40.6 mmol) and malonic acid (4.22 g, 40.6 mmol). The reaction mass was heated to 105°C for 1 h. The reaction mass was diluted with water (20ml) and stirred for 30 min. The precipitated solid was filtered and washed with water. 2N NaOH solution (30 ml) was added to the solid and stirred for 18 hr. The remaining solid was filtered off and ethanol (5 ml) was added to the filtrate was acidified to PH 2 using conc. HCl. The precipitated solid was filtered and washed with water. The solid was dried under reduced pressure to get desired regio isomer in the ratio 50:50 (3 g, 38.6%) as white solid. ^{1}H NMR (400 MHz, DMSO): δ ppm 11.27-11.07 (m, 3H), 10.01 (s, 1H), 7.68-7.65 (d, J = 12 Hz, 1H), 7.41 (t, J = 12 Hz, 1H) 6.91-6.88 (d, J = 12 Hz, 1H), 6.76-6.72 (m, 3H), 5.62-5.60 (d, J = 8 Hz, 2H), 3.92 (s, 3H), 3.72 (s, 3H).

Step 2: Preparation of 2,4-dichloro-5-methoxyquinoline & 2,4-dichloro-7-methoxyquinoline

A solution of 4-hydroxy-5-methoxyquinoline-2(1H)-one & 4-hydroxy-7-methoxyquinoline-2(1H)-one (3 g, 15.70 mmol) in $POCl_3$ (3.66 m, 39.2 mmol) was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get regio isomers as mixture was separated by SFC purification to get desired compound 2,4-dichloro-5-methoxyquinoline (0.7 g, 39%) and 2,4-dichloro-7-methoxyquinoline(required isomer) (1.3 g, 72.6%) as white solid.

2,4-dichloro-7-methoxyquinoline: ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.07-8.04 (d, *J* = 12 Hz, 1H), 7.35-7.34 (m, 2H), 7.28-7.26 (m, 1H), 3.94 (s, 3H);

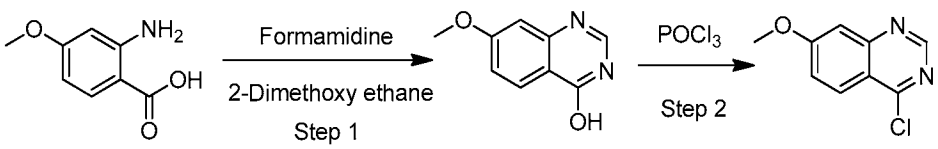
2,4-dichloro-5-methoxyquinoline: ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.66-7.60 (m, 2H), 7.40 (m, 1H), 7.25 (s, 1H), 6.95-6.93 (d, *J* = 8 Hz, 1H), 3.97 (s, 3H).

Step3: Preparation of 4-Chloro-7-methoxy-2-(1H-pyrazol-1-yl) quinoline

Solid pyrazole (3.2 g, 47.36 mmol) was heated to 80°C. Then 2,4-Dichloro-7-methoxyquinoline (3.6 g,15.78 mmol)was added. The reaction mass was heated to 115°C for 3 hr. The reaction mass was cooled to RT and was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get desired compound (2.3 g, 56%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.77 (d, *J* = 2.8 Hz, 1H), 8.18 (s, 1H), 8.10 (d, *J* = 9.2 Hz, 1H), 7.79 (s, 1H), 7.38 (d, *J* = 2.8 Hz, 1H), 7.23 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.53-6.52 (m, 1H), 3.98 (s, 3H); MS: MS *m/z* 260.0 (M^++1).

Scheme: Preparation 4-chloro-7-methoxyquinazoline



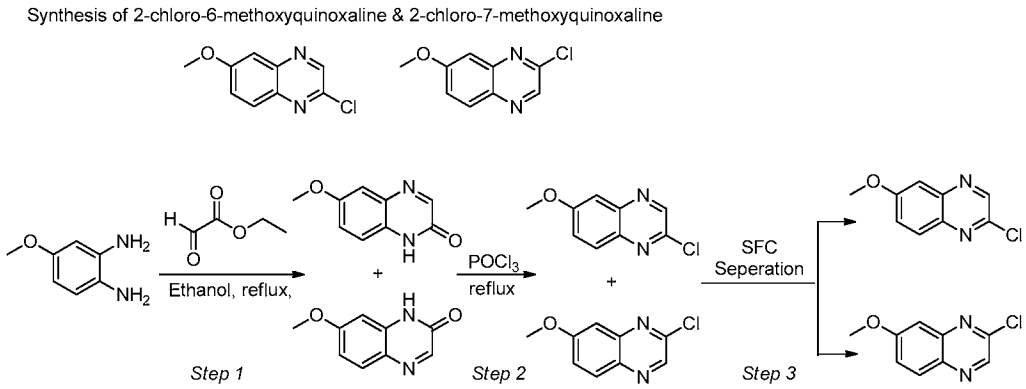
Step 1: Preparation of 7-methoxyquinazolin-4-ol

To a solution of 2-amino-4-methoxy benzoic acid (8.6 g, 51.4 mmol) in 2-dimethoxy ethane (100 ml) was added formamidine (10.71 g, 103 mmol). The reaction mass was heated to 125°C 18 h. The reaction mass was diluted with cold water. The precipitated solid was filtered, washed with water to get crude compound (6.92 g, 74.8%) as pale yellow solid. ^{1}H NMR (400 MHz, DMSO): δ ppm 12.10 (br, s, 1H), 8.06 (s, 1H), 8.03-8.01 (d, J = 8 Hz, 1H), 7.11-7.09 (m, 2H), 3.89 (s, 3H);

Step 2: Preparation of 4-chloro- 7-methoxyquinazoline

A solution of 4,6-dimethoxyisoquinolin-1(2H)-one (1 g, 5.68 mmol) in $POCl_3$ (25 ml) was refluxed for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The combine organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get desired compound (0.87 g, 72.5%) as pale yellow solid. ^{1}H NMR (400 MHz, DMSO): δ ppm 8.52 (br, s, 1H), 8.07-8.05 (d, J = 8 Hz, 1H), 7.20-7.17 (m, 2H), 3.91 (s, 3H); MS: MS *m/z* 195.0 (M^++1).

Scheme 22: Preparation of 2-chloro-6-methoxyquinoxaline and 3-chloro-6-methoxyquinoxaline



Step 1: Preparation of 6-methoxylquinoxalin-2(1H)-one and 7-methoxyquinoxalin-2(1H)-one

To a solution of 4-methoxybenzene-1,2-diamine (5 g, 36.2mmol) in ethanol (50 ml) was added ethyl 2-oxoacetate (4.06 g, 39.8mmol)). The reaction mass was heated at reflux for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate and then evaporated to dryness to get the crude compound. The crude compound was washed with pet ether to get crude compound (5.1 g, 80 % yield) as a mixture of regioisomers (black solid). This crude compound was taken to the next step without separation of isomers. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.17 (s , 1H), 7.98 (s, 1H), 7.70-7.68 (d, J = 8 Hz, 1 H), 7.31-7.30 (d, J = 4 Hz, 1 H), 7.27-7.20 (m, 2 H), 6.93-6.90 (m, 1H), 6.77-6.76 (d, J = 4 Hz, 1 H), 3.84 (s, 3H), 3.83 (s, 3H); MS: MS *m/z* 177.0 (M^++1).

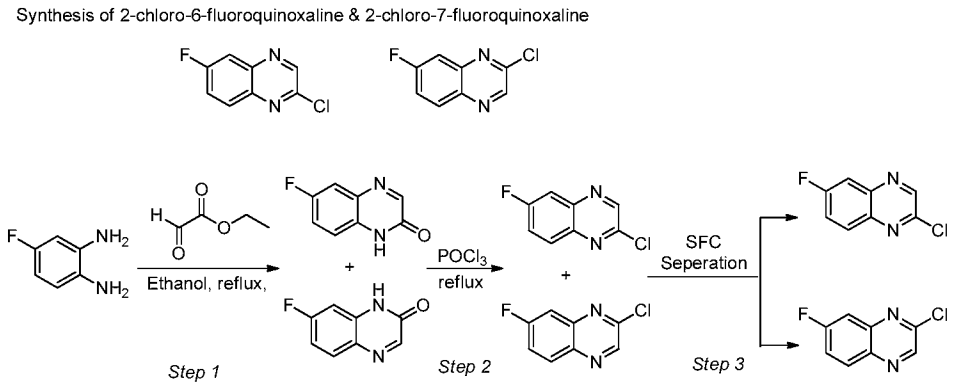
Step 2: Preparation of 2-chloro-6-methoxyquinoxaline and 3-chloro-6-methoxyquinoxaline

A solution of 6-methoxyquinoxalin-2(1H)-one & 7-methoxyquinoxalin-2(1H)-one (3 g, 18.28mmol) in $POCl_3$ (20ml) was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The combine organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to afford mixture of regioisomers (3.7 g). 2 g of the above mixture was separated by SFC purification to afford 2-chloro-7-methoxyquinoxaline (0.7 g, 34.7%) and 2-chloro-7-methoxyquinoxaline (0.9 g, 44.6%) as off white solid.

2-chloro-6-methoxyquinoxaline: ^{1}H NMR (400 MHz, DMSO-d6): δ ppm ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.71 (s, 1H), 7.91-7.89 (d, J = 8 Hz, 1H), 7.46-7.38 (m, 2H), 3.97 (s, 3H); MS: MS *m/z* 194.9(M^++1).

2-chloro-7-methoxyquinoxaline: ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.63 (s, 1H), 7.99-7.96 (d, J = 12 Hz, 1H), 7.43-7.40 (d, J = 12 Hz, 1H), 7.30 (s, 1H), 3.96 (s, 3H); MS: MS *m/z* 194 .9 (M^++1).

Scheme: Preparation of 2-chloro-6 flouroquinoxaline and 3-chloro-6-flouroquinoxaline



Step 1: Preparation of 6-flouroquinoxalin-2(1H)-one and 7-flouroquinoxalin-2(1H)-one

To a solution of 4-flourobenzene-1,2-diamine (5 g, 39.6 mmol) in ethanol (20 ml) was added ethyl 2-oxoacetate (4.45 g, 43.6mmol)). The reaction mass was heated at reflux for overnight. The solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate and then evaporated to dryness to get the crude compound. The crude compound was washed with pet ether to get crude compound (4.6 g, 70 % yield) as a mixture of regioisomers (black solid). This crude compound was taken to the next step without separation of isomers. MS: MS *m/z 162.8* (M^+-1).

Step 2: Preparation of 2-chloro-6-methoxyquinoxaline and 3-chloro-6-methoxyquinoxaline

A solution of 6-flouroquinoxalin-2(1H)-one & 7-flouroquinoxalin-2(1H)-one (3 g, 18.28mmol) in $POCl_3$ (20ml) was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The combine organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to afford regioisomers as a mixture. The above mixture was separated by SFC purification to afford 2-chloro-6-flouroquinoxaline (0.75 g, 44%) and *2*-chloro-7-flouroquinoxaline (0.65 g, 38%) as white solid.

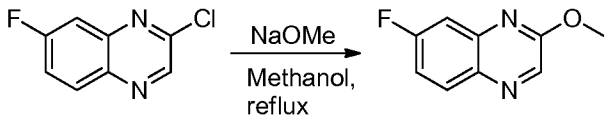
2-chloro-6-flouroquinoxaline*:* ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.75 (s, 1H),

8.14-8.11 (d, *J* = 12 Hz, 1H), 7.67-7.64 (d, *J* = 12 Hz, 1H), 7.59-7.54 (m, 1H); ^{19}F NMR: δ ppm -107.15 (1 F).

2-chloro-7-flouroquinoxaline: ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.79 (s, 1H), 8.05-8.02 (d, *J* = 12 Hz, 1H), 7.77-7.74 (d, *J* = 12 Hz, 1H), 7.62-7.56 (m, 1H); ^{19}F NMR: δ ppm -107.15 (1 F).

Scheme: Preparation of 3-methoxy-6 flouroquinoxaline

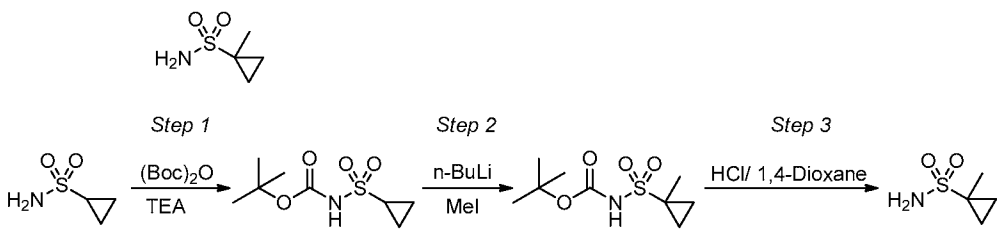
Synthesis of 7-fluoro-2-methoxyquinoxaline



To a solution of 2-chloro-7-fluoroquinoxaline (0.1 g, 0.54 mmol) in methanol (15 ml) was added sodium methoxide (0.29 g, 0.54 mmol) at room temperature under nitrogen atmosphere. The reaction mass was heated at reflux for 3 h. The solvent was evaporated under reduced pressure and the residue was diluted with DCM and washed with water. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude compound 7-fluoro-2-methoxyquinoxaline (0.09 g, 88 % yield) as white solid.^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.41 (s, 1H), 8.01-7.98 (d, *J* = 12 Hz, 1 H), 7.49-7.46 (d, *J* = 12 Hz, 2 H), 7.34-7.3 (m, 1 H), 4.09-4 (s, 3H); ^{19}F NMR: δ ppm -108.99 (1 F).

Scheme 39: Preparation of 1-methylcyclopropane-1-sulfonamide

Synthesis of 1-Methylcyclopropane-1-sulfonamide:



Step 1: Preparation of tert-butyl cyclopropylsulfonylcarbamate

To a solution of cyclopropanesulfonamide (100 g, 82.6 mmol) in DCM (800 ml) was added triethylamine (234 ml, 165 mmol) followed by DMAP (10.28 g, 82.6

mmol) at 0 °C under nitrogen. To this reaction mixture Boc anhydride (247 ml, 107 mmol) in DCM (400 ml) was added slowly. The resulting mixture was stirred for 4 h at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The combine organic layer was washed with 1.5 N HCl solution and 10% $NaHCO_3$ and dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound (143 g, 65.0%) as solid. The crude compound was directly taken for the next step. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 11.08 (s, 1H), 2.90 (m, 1H), 1.48 (s, 9H), 1.06(m, 4H).

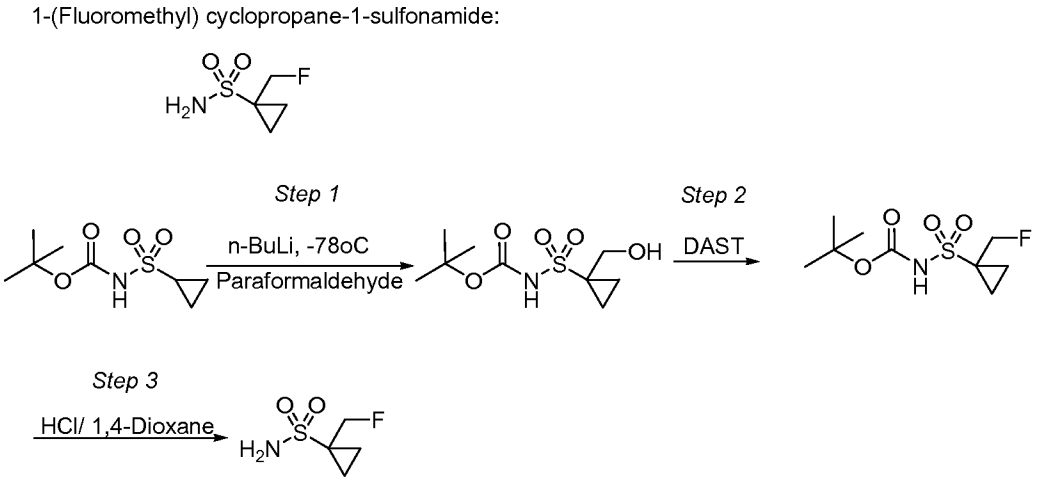
Step 2: Preparation of tert-butyl (1-methylcyclopropyl) sulfonylcarbamate

A solution of tert-butyl cyclopropylsulfonylcarbamate(4.3g, 20 mmol) was dissolved in dry THF (100 ml) and cooled to -78 °C. To this solution was added n-BuLi (17.6 ml, 44 mmol, 2.5 M in hexane) slowly. The reaction mixture was allowed to warm to room temperature over a period of 1.5 h. This mixture was then cooled to -78 °C, and a solution of n-BuLi (20 mmol, 8 ml, 2.5M in hexane) was added, stirred for 1h and a neat solution of methyl iodide (5.68g, 40 mmol) was added. The reaction mixture was allowed to warm to room temperature for overnight, quenched with aqueous saturated NH_4Cl(100 ml) at room temperature. It was extracted with EtOAc(100 ml). The combined organic layer was washed with brine dried on Na_2SO_4, filtered and evaporated under reduced pressure to give a yellow oil which was crystallized from hexane to afford the product as a slightly yellow solid.(3.1 g, 81%). ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 10.97 (s, 1H), 1.44 (s, 12H), 1.35-1.33(m, 2H), 0.93-0.91 (m, 2H).

Step 3: Preparation of 1-methylcyclopropane-1-sulfonamide

A solution of N-ter-butyl-(1-methyl) cyclopropyl-sulfonamide (1.91 g, 10 mmol) was dissolved in 4M HCl in dioxane (30 ml) and the reaction mixture stirred at rt for 16 h. The solvent was removed in vacuo to give a yellow oil which was crystallized from EtOAc/hexane (1:4, 40 ml) to yield 1-methyl-cyclopropylsulfonamide, as a white solid (1.25 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.73 (s, 2H), 1.43 (s, 3H), 1.14-1.12(m, 2H), 0.75-0.73(m, 2H).

Scheme 40: Preparation 1-(Fluoro methyl) cyclopropane-1-sulfonamide



Step 1: Preparation of tert-butyl 1-(hydroxymethyl)cyclopropylsulfonylcarbamate

To a solution of tert-butyl cyclopropylsulfonylcarbamate (30 g, 136 mmol) in 750 mL of THF was added dropwise butyllithium (1.6 M in hexane, 212 mL, 339 mmol) over 30 min at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. Formaldehyde gas was generated from para-formaldehyde (by heating at 180 °C) and was purged into the above reaction mass for 30 min at -30 °C. The reaction was stirred at the same temperature for 1 h, then allowed to warm to room temperature. The reaction was quenched with aqueous ammonium chloride solution and diluted with water. The resulting mass was washed with ethyl acetate and the aqueous layer was acidified to pH ~2 and extracted with ethyl acetate. The combined organics were dried over sodium sulfate, filtered and evaporated under reduced pressure to get desired compound (27 g, 79%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.90 (s*b*, 1H), 4.95 (sb, 1H), 3.75 (s, 2H), 1.42 (s, 9H), 1.27(m, 2H), 1.08 (m, 2 H).

Step 2: Preparation of tert-butyl (1-(fluoromethyl)cyclopropyl)sulfonylcarbamate

To a solution of tert-butyl (1-hydroxymethyl)cyclopropyl) sulfonylcarbamate (10 g, 39.98 mmol) in DCM (150 ml) at -78^{O}C was added DAST (25.7 g, 159 mmol) drop wise. The reaction mass was stirred for 2 hr. The reaction mass was quenched with 1N NaOH solution (200 ml), separated the DCM layer. The DCM layer was washed with NaOH solution (400 ml) ,combined aqueous layer was acidified with 1.5N HCl solution(600ml) and extracted with DCM. The combine

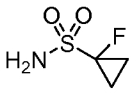
organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get desired compound (9.8 g, 97%) as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.97 (br, s, 1H), 4.74-4.62 (d, J = 48 Hz, 2H), 1.83-1.80 (m, 2H), 1.56-1.44 (m, 9H), 1.20-1.11 (m, 2H).

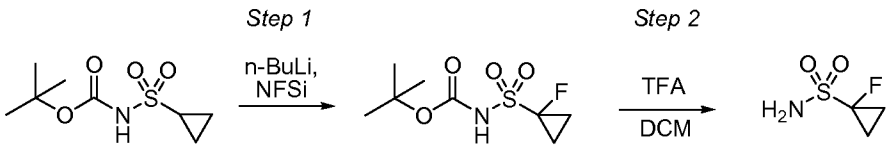
Step 3: Preparation of 1-(fluoromethyl) cyclopropane-1-sulfonamide

To a solution of tert-butyl (1-(fluoromethyl)cyclopropyl)sulfonylcarbamate (19.8 g, 38.7 mmol) in DCM (100 ml) was added TFA (30 ml, 387 mmol) drop wise at room temperature. The reaction mass was stirred for 2 hr. The reaction mass was evaporated under reduced pressure to get desired compound (6 g, 100%) as off white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 4.78-4.66 (d, J = 48 Hz, 2H), 2.61 (br, s, 1H), 1.59-1.56 (m, 2H), 1.13-1.10 (m, 2H).

Scheme 41: Preparation 1-Fluoro cyclopropane-1-sulfonamide

1-fluorocyclopropane-1-sulfonamide





Step 1: Preparation of tert-butyl (1-fluorocyclopropyl)sulfonylcarbamate

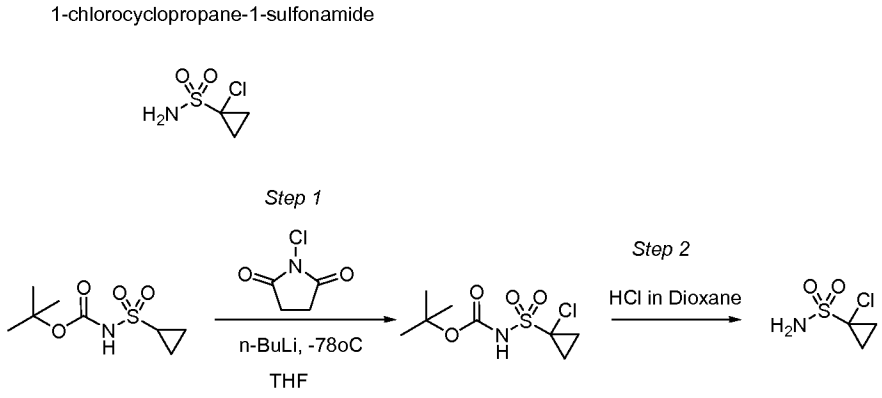
A solution of *tert-butyl cyclopropyl sulfonyl carbamate* (25 g, 113mmol) in THF (750 mL) was added n-BuLi (156mL, 249 mmol, 1.6 M in hexane) at -78 °C. The reaction mixture was stirred for 1 h at -78° C, and NFSi (42.8 g, 136 mmol) in THF (250 ml) was added drop wise. The reaction mass was stirred at 0°C for 2 h, then allowed to warm to room temperature and stirred for overnight. The reaction mass was diluted with Ethyl acetate, quenched with saturated aqueous NH_4Cl (700mL) at room temperature and separated the Ethyl acetatelayer. The combined organic layer was evaporated under reduced pressure. To the residue ether (500 ml) was added, washed with 1M NaOH solution (600 ml). Then aqeous layer was acidified to PH 2 using 1.5 N HCl solution (700 ml) and extracted with DCM. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under

reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (10% ethyl acetate in pet ether) to get desired (5.7 g, 21%) as pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.14 (s, br, 1H), 1.80-1.76 (m, 2H), 1.56-1.49 (m, 11H).

Step 2: Preparation of 1-fluorocyclopropane-1-sulfonamide

To a solution of tert-butyl (1-fluorocyclopropyl)sulfonylcarbamate (11.1 g, 46.4 mmol) in DCM (110 ml) was added TFA (52.9 g, 464 mmol) drop wise at room temperature. The reaction mass was stirred for 2 hr. The reaction mass was evaporated under reduced pressure to get desired compound (5.93 g, 92%) as a light red solid. ^{1}H NMR (400 MHz, DMSO): δ ppm 7.51 (br, s, 2H), 1.52-1.45 (m, 2H), 1.45-1.37 (m, 2H).

Scheme 42: Preparation 1-chloro cyclopropane-1-sulfonamide



Step 1: Preparation of tert-butyl (1-chlorocyclopropyl) sulfonylcarbamate

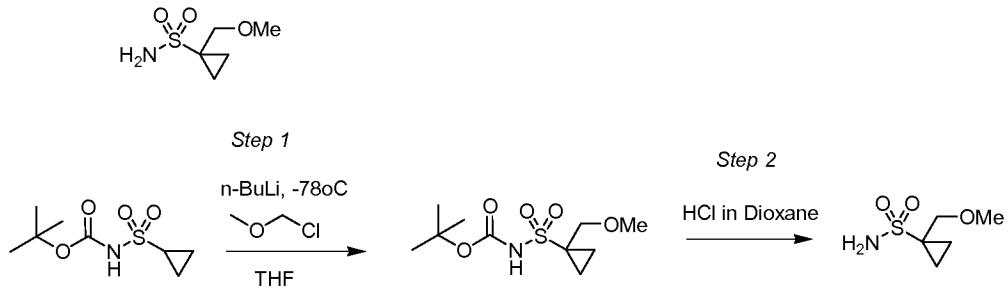
A solution of tert-butyl cyclopropyl sulfonyl carbamate (2 g, 9.04 mmol) in THF (20 ml) was added n-BuLi (12.7 ml, 20.34 mmol, 1.6 M in hexane) at -78 ° C. The reaction mixture was stirred for 1 h at -78° C and N-chlorosuccinamide (1.69 g, 12.65 mmol) in THF (20 ml) was added drop wise. The reaction mass was stirred at -78°C for 3 h. The reaction mass was diluted with ice water, acidified to P^H 4 using 1.5 N HCl solution and extracted with DCM. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (60% ethyl acetate in pet ether) to get desired (1 g, 43.3%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.09 (br,s, 1H), 2.07-2.03 (m, 2H), 1.53-1.49 (m, 11H); MS: MS *m/z 254.05* (M^+-1).

Step 2: Preparation of 1-chlorocyclopropane-1-sulfonamide

To tert-butyl (1-chlorocyclopropyl) sulfonylcarbamate (3.2 g, 12.51 mmol) was added HCl in 1,4-Dioxane (40 ml, 4 M solution) at room temperature. The reaction mass was stirred for 2 hr. The reaction mass was evaporated under reduced pressure to get desired compound (1.8 g, 92%) as white solid. ^{1}H NMR (400 MHz, DMSO): δ ppm 7.43 (br, s, 2H), 1.62-1.58 (m, 2H), 1.45-1.41 (m, 2H).

Scheme 43: Preparation 1-chloro cyclopropane-1-sulfonamide

1-(methoxymethyl)cyclopropane-1-sulfonamide



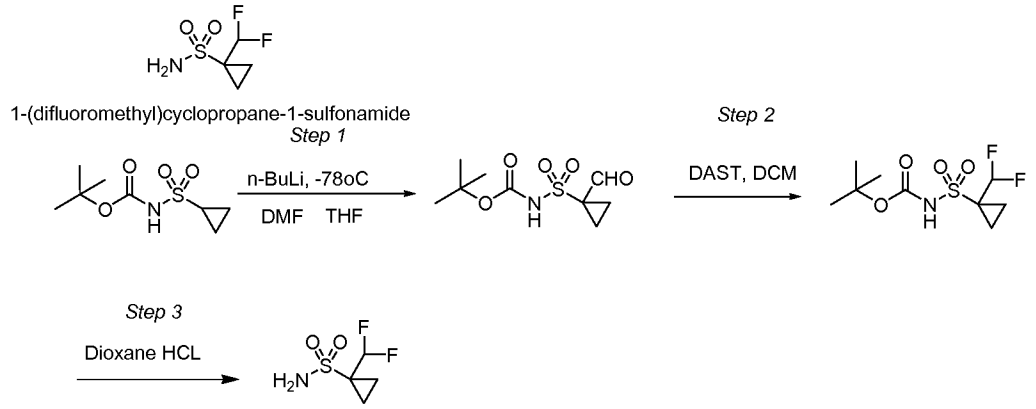
Step 1: Preparation of tert-butyl (1-(methoxymethyl)cyclopropyl)sulfonylcarbamate

A solution of tert-butyl cyclopropyl sulfonyl carbamate (2 g, 9.04 mmol) in THF (60 ml) was added n-BuLi (12.77 ml, 20.43 mmol, 1.6 M in hexane) at -78 ° C. The reaction mixture was stirred for 1 h at -78° C and Chloromethyl methyl ether (0.84 g, 10.48 mmol) was added drop wise. The reaction mass was allowed to warm to room temperature and stirred for overnight. The reaction mass was diluted with ice water, acidified to P^H 3 using 1.5 N HCl solution and extracted with DCM. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound (2.2 g, 92%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.35 (br,s, 1H), 3.70 (s, 2H), 3.35 (s, 3H), 1.53-1.44 (m, 11H), 1.06-1.03 (m, 2H).

Step 2: Preparation of 1-(methoxymethyl) cyclopropane-1-sulfonamide

To tert-butyl (1-(methoxymethyl)cyclopropyl)sulfonylcarbamate (2.2 g, 8.29 mmol) was added HCl in 1,4-Dioxane (20 ml, 4M solution) at room temperature. The reaction mass was stirred for 2 hr. The reaction mass was evaporated under reduced pressure to get desired compound (1.2 g, 88%) as white solid. ^{1}H NMR (400 MHz, DMSO): δ ppm 6.68 (br, s, 2H), 3.62 (s, 2H), 3.27 (s, 3H), 1.22-1.09 (m, 2H), 0.96-0.91 (m, 2H).

Scheme 44: Preparation 1-(difluoro methyl) cyclopropane-1-sulfonamide



Step 1: Preparation of tert-butyl (1-formylcyclopropyl) sulfonylcarbamate

A solution of *tert-butyl cyclopropyl sulfonyl carbamate* (10 g, 45.2 mmol) in THF (150 ml) was added n-BuLi (70.6 ml, 113 mmol, 1.6 M in hexane) at -78 °C. The reaction mixture was stirred for 1 h at -78° C, and DMF (6.6 g, 90 mmol) was added drop wise. The reaction mass was stirred at -78°C for 1 h. The reaction mass was diluted water (100 ml) and extracted with Ethyl acetate. Then aqueous layer was acidified to P^H 2 using 1.5 N HCl solution and extracted with DCM. The combine organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get desired compound (10 g, 89%) as white solid. ^{1}H NMR (400 MHz, DMSO): δ ppm 11.70(br, s, 1H), 9.95 (s, 1H), 1.80-1.70 (m, 4H), 1.42 (m, 9H); MS: MS *m/z 248.08* (M^+-1).

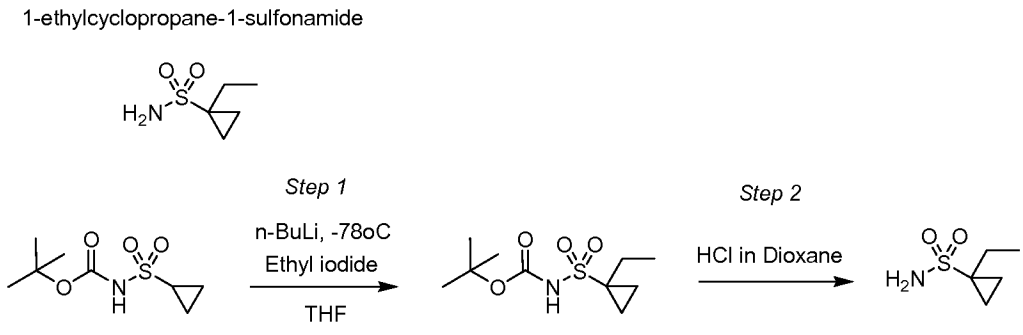
Step 2: Preparation of tert-butyl (1-(difluoromethyl)cyclopropyl)sulfonylcarbamate

To a solution of tert-butyl (1-formylcyclopropyl) sulfonylcarbamate (1 g, 4.01 mmol) in DCM (10 ml) at -78°C was added DAST (1.94 g, 12.03 mmol) drop wise. The reaction mass was stirred for 4 hr at room temperature. The reaction mass was quenched with 1N NaOH solution (20 ml), separated the DCM layer. TheDCM layer was washed with NaOH solution (40 ml), combined aqueous layer was acidified with 1.5N HCl solution (60ml) and extracted with DCM. The combine organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get desired compound (0.4 g, 36.8%) as light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.25 (br, s, 1H), 6.43 (t, J = 56 Hz, 1H), 1.77 (m, 2H), 1.51 (m, 9H), 1.42-1.41 (m, 2H); ^{19}F NMR: δ ppm -120.81(2F).

Step 3: Preparation of 1-(difluoromethyl) cyclopropane-1-sulfonamide

To tert-butyl (1-(fluoromethyl) cyclopropyl) sulfonylcarbamate (1.60 g, 5.90 mmol) was added HCl in 1,4-Dioxane (10 ml, 4M solution) drop wise at room temperature. The reaction mass was stirred for 2 hr. The reaction mass was evaporated under reduced pressure to get desired compound (0.97 g, 96%) as off white solid. ^{1}H NMR (400 MHz, DMSO): δ ppm 7.26 (br, s, 2H), 6.49 (t, J = 136 Hz, 1H), 1.33-1.19 (m, 4H); ^{19}F NMR: δ ppm -118.52(2F).

Scheme 45: Preparation 1-ethyl cyclopropane-1-sulfonamide



Step 1: Preparation of tert-butyl (1-ethyl cyclopropyl) sulfonylcarbamate

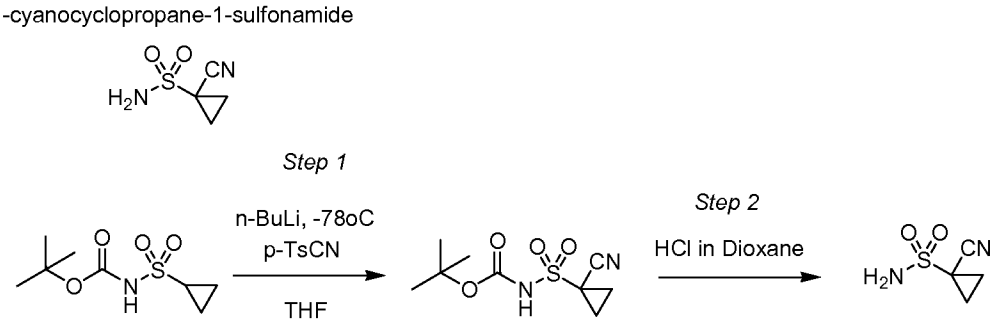
A solution of tert-butyl cyclopropyl sulfonyl carbamate (10 g, 63.6 mmol) in THF (100 ml) was added n-BuLi (59.6 ml, 95 mmol, 1.6 M in hexane) at -78 °C. The reaction mixture was stirred for 1 h at -78° C and ethyl iodide (49.6 g, 318 mmol) was added drop wise. The reaction mass was allowed to warm to room temperature and stirred for overnight. The reaction mass was qunched with aqueous NH_4Cl solution and extracted with DCM. The combine organic layer was washed with brine solution, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound (4.8 g, 40.7%) as pale yellow solid. ^{1}H NMR (400 MHz, DMSO): δ ppm 1.80-1.77 (m, 2H), 1.49-1.36 (m, 12H), 0.95 (t, J = 8 Hz, 3H), 0.89-0.88 (m, 2H).

Step 2: Preparation of 1-ethyl cyclopropane-1-sulfonamide

To tert-butyl (1-ethyl cyclopropyl) sulfonylcarbamate (4.8 g, 19.25 mmol) was added HCl in 1,4-Dioxane (20 ml, 4M solution) at room temperature. The reaction mass was stirred for 3 hr. The reaction mass was evaporated under reduced pressure to get desired compound (2.5 g, 87%) as brown semi solid. ^{1}H NMR (400 MHz, DMSO): δ ppm 6.70 (br, s, 2H), 1.85-1.81 (m, 2H), 1.10-1.08 (m, 2H), 0.95 (t,

J = 8 Hz, 3H), 0.89-0.87 (m, 2H).

Scheme 46: Preparation 1-cyno cyclopropane-1-sulfonamide



Step 1: Preparation of tert-butyl (1-cyano cyclopropyl) sulfonylcarbamate

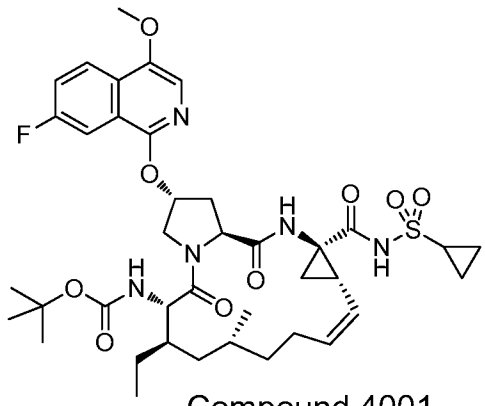
A solution of tert-butyl cyclopropyl sulfonyl carbamate (1 g, 4.52 mmol) in THF (10 ml) was added n-BuLi (6.38 ml, 10.21 mmol, 1.6 M in hexane) at -78 °C. The reaction mixture was stirred for 1 h at -78° C and p-TsCN(0.98 g, 5.42 mmol) was added drop wise. The reaction mass was allowed to warm to room temperature and stirred for overnight. The reaction mass was quenched with aqueous NH_4Cl solution and extracted with ethyl acetate. The combine organic layer was washed with brine solution, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound (0.5 g, 44.9%) as semi solid. ^{1}H NMR (400 MHz, DMSO): δ ppm 1.89-1.76 (m, 2H), 1.51-1.45 (m, 12H).

Step 2: Preparation of 1-cyano cyclopropane-1-sulfonamide

To tert-butyl (1-ethyl cyclopropyl) sulfonylcarbamate (0.5 g, 2.03 mmol) was added HCl in 1,4-Dioxane (5 ml, 4M solution) at room temperature. The reaction mass was stirred for 3 hr. The reaction mass was evaporated under reduced pressure to get desired compound (0.1 g, 33.7%) as off white solid. ^{1}H NMR (400 MHz, DMSO): δ ppm 7.78 (br, s, 2H), 1.79-1.76 (m, 2H), 1.59-1.56 (m, 2H).

Preparation of Compound 4001

tert-butyl tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-7-ethyl-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

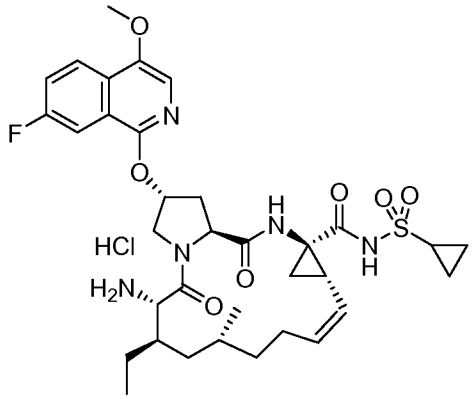


Compound 4001

To a solution of tert-butyl (2R,6S,7R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-7-ethyl-2-hydroxy-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate (300 mg, 0.49 mmole) and 1,7-difluoro-4-methoxyisoquinoline (95.9 mg, 0.49 mmole) in DMSO (5 mL) was added t-BuOK (274 mg, 2.45 mmol, 1M solution in THF, 2.74 mL) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mass was quenched with aqueous citric acid solution and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with water, brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC to get 138 mg (36%) of desired compound as white solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 0.84 (d, *J*=14.81 Hz, 3H), 1.03 (s, 4H) 1.06-1.15 (m, 9H), 1.19-1.36 (m, 3H), 1.40-1.63 (m, 6H), 1.78 (dd, *J*=8.16, 5.65 Hz, 1H), 1.90 - 2.05 (m, 2 H), 2.37 - 2.48 (m, 2H), 2.68-2.78 (m, 2 H), 2.91-2.96 (m, 1 H), 3.98-4.04 (m, 3 H), 4.11 (s, 1H), 4.62 (dd, *J*=10.29, 7.03 Hz, 1, H), 4.77 (s, 1, H), 5.06 (br. s., 1H), 5.57 - 5.67 (m, 1H),

5.85 (br. s., 1H), 6.60 (d, *J*=9.03 Hz, 1 H), 7.49 - 7.58 (m, 2 H), 7.73 (dd, *J*=9.54, 2.51 Hz, 1 H), 8.17 (dd, *J*=9.16, 5.40 Hz, 1 H); MS: MS *m/z* 787.4 (M^++1).

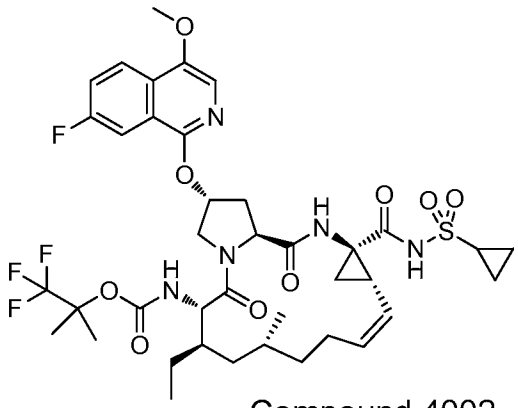
Preparation of (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(cyclopropylsulfonyl)-7-ethyl-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride



A solution of Compound 4001 (100 mg, 0.10 mmole) in 4M HCl in dioxane was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure to get crude compound (69 mg, 96%). The crude compound was washed with diethyl ether and taken to the next step without further purification. MS: MS *m/z* 686.7 (M^++1).

Preparation of Compound 4002

1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-7-ethyl-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

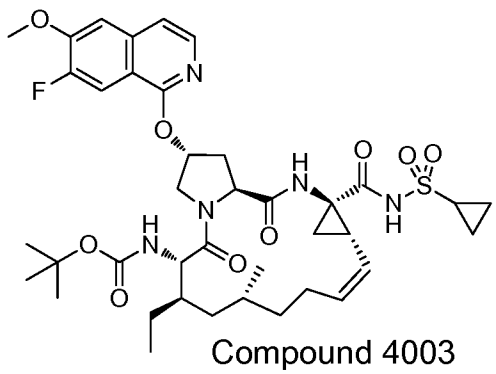


Compound 4002

To a solution of *(2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(cyclopropylsulfonyl)-7-ethyl-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride* (95 mg, 0.13 mmol) in DCM (4 mL) was added DIPEA (0.07 mL, 0.39 mmole) followed by carbonic acid pyridin-2-yl ester 2,2,2-trifluoro-1,1-dimethyl-ethyl ester (32.37 mg, 0.13 mmole) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The reaction mass was diluted with DCM and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC to get compound 4002 (18.5 mg, 17%) as white solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 0.80 - 0.90 (m, 3 H), 0.97 - 1.06 (m, 4 H), 1.09 - 1.18 (m, 10 H), 1.22 - 1.39 (m, 3 H), 1.49 - 1.65 (m, 6 H), 1.78 (dd, *J*=8.28, 5.52 Hz, 1 H), 1.97 (d, *J*=10.54 Hz, 2 H), 2.38 - 2.49 (m, 2 H), 2.66 - 2.79 (m, 2 H), 2.88 - 2.97 (m, 1 H), 3.98 - 4.07 (m, 5 H), 4.61 - 4.68 (m, 1 H), 4.77 (s, 1 H), 5.08 (br. s., 1 H), 5.63 (td, *J*=10.04, 5.77 Hz, 1 H), 5.85 (br. s., 1 H), 7.52 - 7.61 (m, 2 H), 7.75 (dd, *J*=9.54, 2.51 Hz, 1 H), 8.19 (dd, *J*=9.16, 5.40 Hz, 1 H); MS: MS *m/z* 841.4 (M^++1).

Preparation of Compound 4003

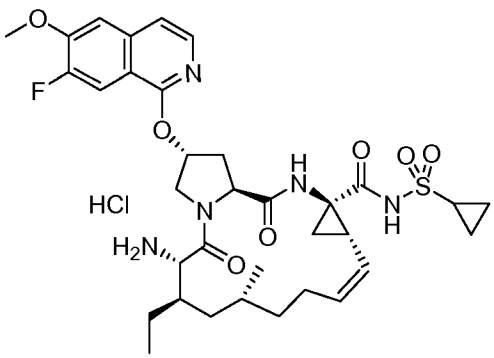
tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-7-ethyl-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate



Compound 4003

Compound 4003 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 0.85 (d, *J*=15.06 Hz, 3 H), 1.02 (m, 7 H), 1.06 - 1.19 (m, 7 H), 1.29 (t, *J*=9.16 Hz, 3 H), 1.42 - 1.63 (m, 6 H), 1.77 (dd, *J*=8.28, 5.27 Hz, 1 H), 1.96 (s, 3 H), 2.37 - 2.49 (m, 2 H), 2.66 - 2.78 (m, 2 H), 2.92 (br. s., 1 H), 4.01 (br. s., 5 H), 4.09 (d, *J*=11.04 Hz, 1 H), 4.58 - 4.65 (m, 1 H), 4.75 (d, *J*=11.29 Hz, 1 H), 5.15 (br. s., 1 H), 5.56 - 5.65 (m, 1 H), 5.90 (br. s., 1 H), 7.26 - 7.33 (m, 1 H), 7.40 (s, 1 H), 7.78 (s, 1 H), 7.92 - 7.93 (m, 1 H); MS: MS *m/z* 786.4 (M^++1).

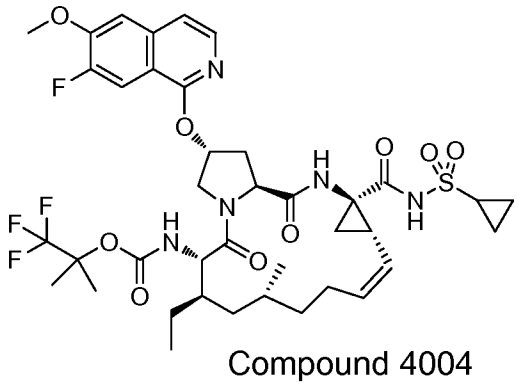
Preparation of (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(cyclopropylsulfonyl)-7-ethyl-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride



A solution of Compound 4003 (100 mg, 0.10 mmole) in 4M HCl in dioxane was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure to get crude compound (70.6 mg, 98%). The crude compound was washed with diethyl ether and taken to the next step without further purification. MS: MS *m/z* 687.2 (M^++1).

Preparation of Compound 4004

1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-7-ethyl-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate



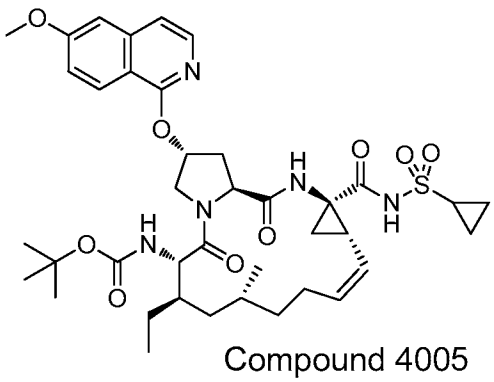
Compound 4004

Compound 4004 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 0.83 (t, *J*=7.40 Hz, 3 H), 0.99 - 1.05 (m, 4 H), 1.08

- 1.17 (m, 6 H), 1.30 - 1.42 (m, 5 H), 1.52 - 1.64 (m, 5 H), 1.78 (dd, *J*=8.41, 5.65 Hz, 1 H), 1.98 (t, *J*=10.67 Hz, 2 H), 2.43 (ddd, *J*=13.74, 10.23, 3.89 Hz, 2 H), 2.68 - 2.79 (m, 2 H), 2.90 - 2.98 (m, 1 H), 3.98 - 4.08 (m, 5 H), 4.64 (dd, *J*=10.04, 7.03 Hz, 1 H), 4.73 (d, *J*=10.54 Hz, 1 H), 5.04 (t, *J*=10.04 Hz, 1 H), 5.63 (td, *J*=10.23, 5.90 Hz, 1 H), 5.85 - 5.93 (m, 1 H), 7.31 (d, *J*=5.77 Hz, 1 H), 7.40 (d, *J*=8.28 Hz, 1 H), 7.77 (d, *J*=11.54 Hz, 1 H), 7.93 - 7.98 (m, 1 H), 7.95 (d, *J*=6.02 Hz, 1 H); MS: MS *m/z* 841.2 (M^++1).

Preparation of Compound 4005

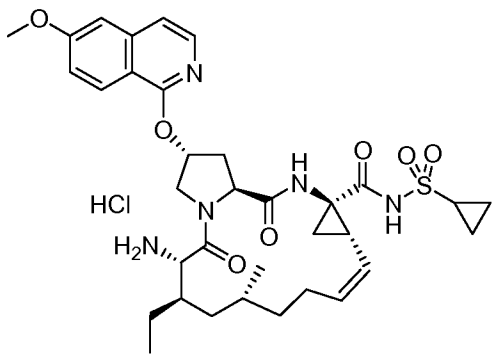
tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-7-ethyl-2-(6-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate



Compound 4005

Compound 4005 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 0.79 - 0.92 (m, 4 H), 1.03 (m, 4 H), 1.16 (s, 9 H) 1.28 - 1.37 (m, 2 H), 1.44 - 1.67 (m, 6 H), 1.78 (d, *J*=5.52 Hz, 1 H), 1.85 - 2.02 (m, 2 H), 2.43 (t, *J*=10.16 Hz, 2 H), 2.68 - 2.79 (m, 2 H), 2.87 - 2.99 (m, 1 H), 3.94 (s, 3 H), 4.01 - 4.17 (m, 2 H), 4.51 - 4.63 (m, 1 H), 4.75 (d, *J*=11.04 Hz, 1 H), 5.08 (br. s., 1 H), 5.56 - 5.67 (m, 1 H), 5.89 (br. s., 1 H), 7.09 (dd, *J*=9.03, 2.26 Hz, 1 H), 7.19 (d, *J*=2.26 Hz, 1 H), 7.26 (d, *J*=5.77 Hz, 1 H), 7.93 (s, 1 H), 8.10 (d, *J*=9.29 Hz, 1 H); MS: MS *m/z* 768.4 (M^++1).

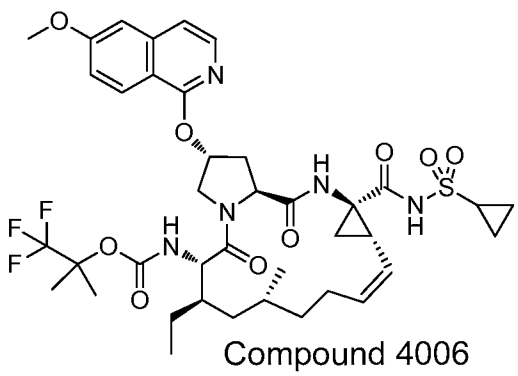
Preparation of (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(cyclopropylsulfonyl)-7-ethyl-2-(6-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride



A solution of Compound 4005 (100 mg, 0.13 mmole) in 4M HCl in dioxane was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure to get crude compound (89 mg, 97%). The crude compound was washed with diethyl ether and taken to the next step without further purification. MS: MS *m/z* 669.1 (M^++1).

Preparation of Compound 4006

1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-7-ethyl-2-(6-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

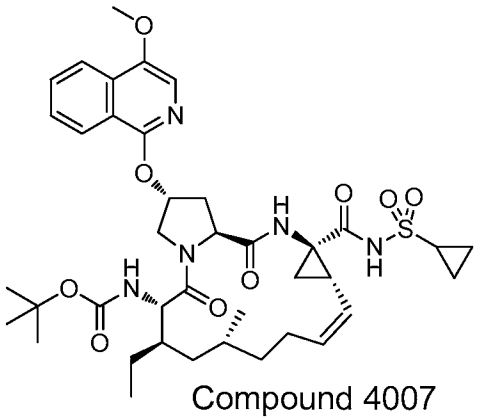


Compound 4006

Compound 4006 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 0.83 (d, *J*=15.06 Hz, 3 H), 0.94 - 1.18 (m, 11 H), 1.28 - 1.41 (m, 5 H), 1.43 - 1.64 (m, 7 H), 1.75 - 1.81 (m, 1 H), 1.92 - 2.05 (m, 2 H), 2.36 - 2.50 (m, 2 H), 2.66 - 2.78 (m, 2 H), 2.88 - 2.98 (m, 1 H), 3.95 (s, 3 H), 3.99 - 4.09 (m, 2 H), 4.65 (dd, *J*=10.29, 7.03 Hz, 1 H), 4.72 - 4.80 (m, 1 H), 5.04 (t, *J*=9.79 Hz, 1 H), 5.63 (td, *J*=10.16, 6.02 Hz, 1 H), 5.88 (d, *J*=6.27 Hz, 1 H), 7.12 (dd, *J*=9.03, 2.51 Hz, 1 H), 7.22 (d, *J*=2.51 Hz, 1 H), 7.28 (d, *J*=6.02 Hz, 1 H), 7.90 - 7.96 (m, 1 H), 8.09 (d, *J*=9.04 Hz, 1 H), 9.00 (s, 1 H); MS: MS *m/z* 822.2 (M^++1).

Preparation of Compound 4007

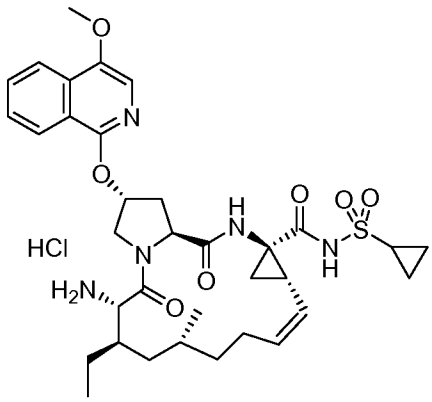
tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-7-ethyl-2-(4-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate



Compound 4007

Compound 4007 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 0.82 - 0.86 (m, 4 H), 1.01-1.12 (m, 7 H), 1.16 (s, 9 H), 1.27 - 1.34 (m, 7 H), 1.51 - 1.58 (m, 1 H), 1.60-1.95 (m, 2 H), 2.42-2.43 (m, 2 H), 2.71-2.75 (m, 2 H), 2.93 (m, 1 H), 4.02-4.04 (m, 4 H), 4.11 (m, 1 H), 4.61 - 4.62 (m, 1 H), 4.75 - 4.84 (m, 1 H), 5.04 (m,1 H), 5.84 (m, 1 H), 6.58-6.61 (m, 1 H), 7.55-7.57 (m, 2 H), 7.72 (m, 1 H), 8.09-8.14 (m, 2 H); MS: MS *m/z* 768.5 (M^++1).

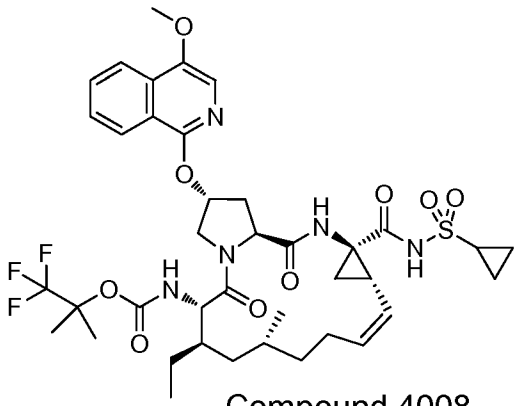
Preparation of (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(cyclopropylsulfonyl)-7-ethyl-2-(4-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride



A solution of Compound 4007 (100 mg, 0.13 mmole) in 4M HCl in dioxane was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure to get crude compound (70 mg, 99%). The crude compound was washed with diethyl ether and taken to the next step without further purification. MS: MS *m/z* 668.6 (M^++1).

Preparation of Compound 4008

1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-7-ethyl-2-(4-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

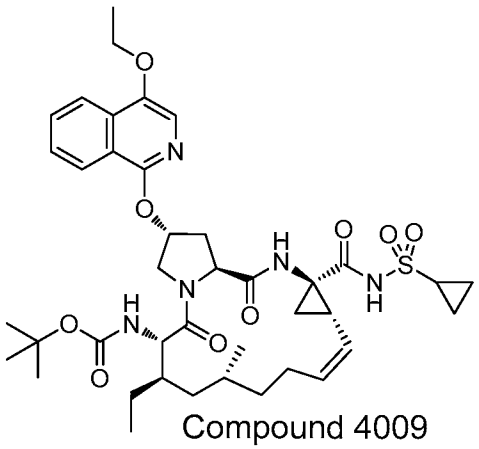


Compound 4008

Compound 4008 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 0.80 (d, *J*=15.06 Hz, 3 H), 0.89 (s, 3 H), 0.97 - 1.16 (m, 8 H), 1.25 - 1.36 (m, 6 H), 1.41 - 1.61 (m, 7 H), 1.76 (dd, *J*=8.28, 5.52 Hz, 1 H), 1.90 - 2.02 (m, 2 H), 2.41 (ddd, *J*=13.87, 10.10, 3.89 Hz, 2 H), 2.66 - 2.77 (m, 2 H), 2.87 - 2.96 (m, 1 H), 3.93 - 4.04 (m, 5 H), 4.63 (dd, *J*=10.16, 6.90 Hz, 1 H), 4.96 - 5.07 (m, 1 H), 5.60 (td, *J*=9.98, 6.15 Hz, 1 H), 5.82 (br. s., 1 H), 7.52 - 7.58 (m, 2 H), 7.72 (ddd, *J*=8.28, 7.03, 1.25 Hz, 1 H), 8.12 (dd, *J*=12.17, 8.41 Hz, 2 H); ^{19}F NMR: δ ppm -85.11 (3 F); MS: MS *m/z* 822.52 (M^{+}+1).

Preparation of Compound 4009

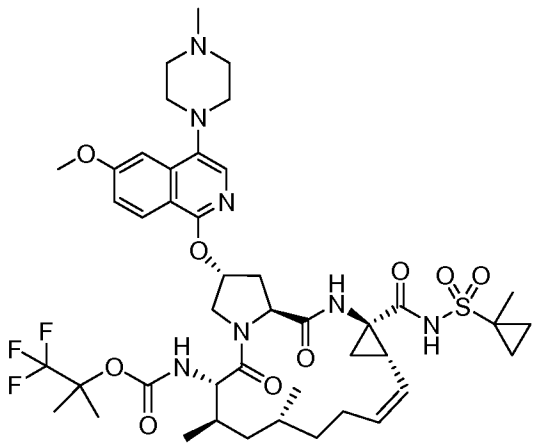
tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(4-ethoxyisoquinolin-1-yloxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate



Compound 4009

Compound 4009 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1. MS: MS *m/z* 783.3 (M^++1).

Preparation of Compound 4013



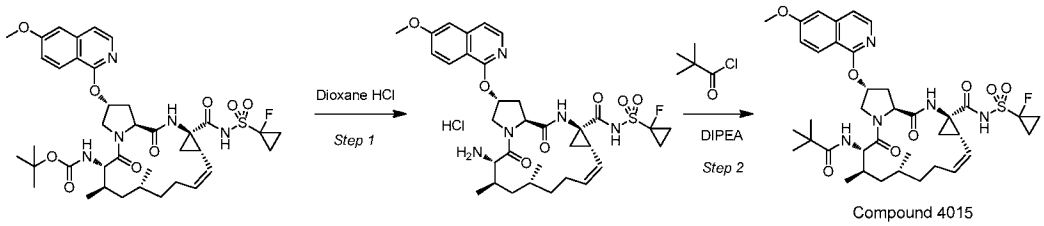
Compound 4013

Compound 4013 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4013: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(6-methoxy-4-(4-methylpiperazin-1-yl)isoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-

5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.05 (s, 1 H) 8.11 - 8.17 (m, 1 H) 7.79 (s, 1 H) 7.41 (d, *J*=2.51 Hz, 1 H) 7.35 (d, *J*=8.03 Hz, 1 H) 7.18 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.87 (br. s., 1 H) 5.63 (td, *J*=10.48, 5.40 Hz, 1 H) 5.00 (t, *J*=9.91 Hz, 1 H) 4.61 - 4.75 (m, 2 H) 3.97 - 4.06 (m, 4 H) 3.78 - 3.84 (m, 1 H) 3.65 - 3.72 (m, 2 H) 3.45 - 3.57 (m, 4 H) 3.19 - 3.28 (m, 2 H) 3.06 (s, 3 H) 2.68 - 2.76 (m, 2 H) 2.44 (ddd, *J*=13.80, 10.04, 4.27 Hz, 2 H) 1.77 (dd, *J*=8.28, 5.52 Hz, 1 H) 1.64 - 1.70 (m, 1 H) 1.57 (dd, *J*=9.41, 5.65 Hz, 1 H) 1.39 - 1.53 (m, 6 H) 1.20 - 1.37 (m, 6 H) 0.96 - 1.05 (m, 9 H) 0.79 - 0.94 (m, 4 H); MS: MS *m/z* 920.9 (M^++1).

Scheme:



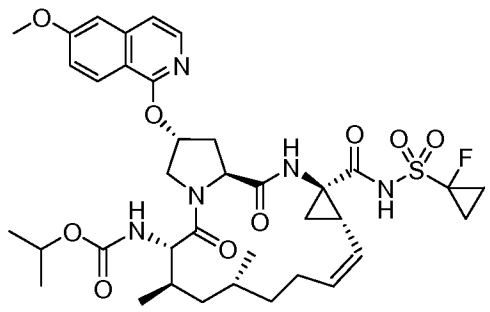
Step 1: Preparation of *(2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(1-fluorocyclopropylsulfonyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride*

A solution of tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-fluorocyclopropyl)sulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate (30 mg, 0.039 mmol) in 4M HCl in dioxane (5 ml 4M solution) was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure to get crude compound (23 mg, 90%) as brown solid. The crude compound was washed with diethyl ether and taken to the next step without further purification. MS: MS *m/z* 772.8.0(M^+-36).

Step 2: Preparation of Compound 4015

To a solution of *(2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(1-fluorocyclopropylsulfonyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride* (23 mg, 0.034 mmol) in DCM was added pivaloyl chloride (4 mg, 0.034 mmol) followed byy DIPEA (15 mg, 0.12 mmol) at room temperature. The reaction mass was stirred at room temperature for 30 min. The reaction mass was diluted with DCM and washed with water. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude compound. The crude compound was purified by prep-HPLC to get 10 mg (40%) of Compound 4015 as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.97 (s, 1 H) 8.05 (d, *J*=9.29 Hz, 1 H) 7.89 (d, *J*=5.77 Hz, 1 H) 7.25 (d, *J*=6.02 Hz, 1 H) 7.17 - 7.20 (m, 1 H) 7.07 (dd, *J*=9.03, 2.26 Hz, 1 H) 5.86 - 5.90 (m, 1 H) 5.57 - 5.64 (m, 1 H) 4.98 (t, *J*=10.04 Hz, 1 H) 4.53 - 4.63 (m, 2 H) 4.27 (dd, *J*=10.67, 8.66 Hz, 1 H) 4.05 (dd, *J*=11.54, 3.76 Hz, 1 H) 3.92 (s, 3 H) 2.73 (t, *J*=8.16 Hz, 2 H) 2.35 - 2.46 (m, 2 H) 1.94 - 2.06 (m, 2 H) 1.69 - 1.82 (m, 3 H) 1.44 - 1.66 (m, 6 H) 1.19 - 1.38 (m, 3 H) 0.96 - 1.02 (m, 11 H) 0.93 (d, *J*=6.53 Hz, 3 H) 0.80 - 0.88 (m, 1 H); MS: MS *m/z* 756.0 (M^++1).

Preparation of Compound 4016

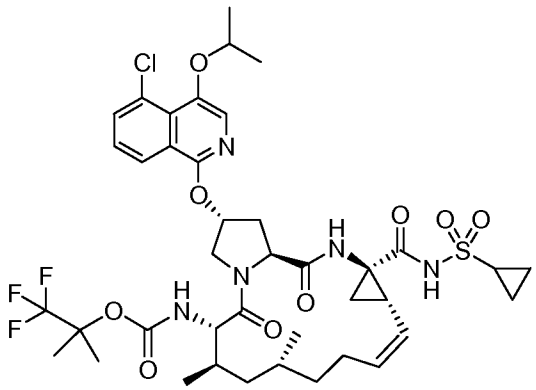


Compound 4016

Compound 4016 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4016: isopropyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.02 (s, 1 H) 8.12 (d, *J*=9.03 Hz, 1 H) 7.92 (d, *J*=6.02 Hz, 1 H) 7.29 (d, *J*=6.02 Hz, 1 H) 7.22 (d, *J*=2.26 Hz, 1 H) 7.12 (d, *J*=9.03 Hz, 1 H) 5.91 (br. s., 1 H) 5.57 - 5.65 (m, 1 H) 4.94 - 5.02 (m, 1 H) 4.70 (d, *J*=11.04 Hz, 1 H) 4.62 (dd, *J*=9.79, 7.03 Hz, 1 H) 4.30 - 4.38 (m, 1 H) 4.05 (dd, *J*=11.29, 3.51 Hz, 1 H) 3.90 - 3.96 (m, 4 H) 2.69 - 2.79 (m, 2 H) 2.33 - 2.49 (m, 2 H) 1.99 (br. s., 1 H) 1.89 (d, *J*=5.52 Hz, 1 H) 1.72 - 1.83 (m, 3 H) 1.56 - 1.70 (m, 2 H) 1.45 - 1.54 (m, 4 H) 1.20 - 1.33 (m, 2 H) 1.08 (d, *J*=6.27 Hz, 3 H) 1.00 (dd, *J*=11.29, 6.53 Hz, 6 H) 0.92 (d, *J*=6.27 Hz, 3 H) 0.81 - 0.88 (m, 1 H); MS: MS *m/z* 758.9 (M^++1).

Preparation of Compound 4017



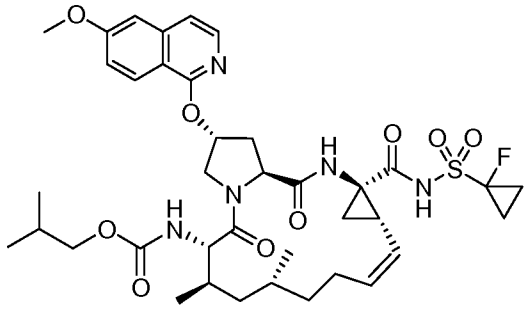
Compound 4017

Compound 4017 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4017: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(5-chloro-4-isopropoxyisoquinolin-1-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-

a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17 (dd, *J*=8.28, 1.00 Hz, 1 H) 7.72 - 7.77 (m, 2 H) 7.45 (t, *J*=7.91 Hz, 1 H) 5.83 (br. s., 1 H) 5.59 - 5.66 (m, 1 H) 5.04 (t, *J*=9.91 Hz, 1 H) 4.77 (d, *J*=11.80 Hz, 1 H) 4.64 - 4.70 (m, 2 H) 3.98 (dd, *J*=11.54, 3.26 Hz, 1 H) 3.76 - 3.82 (m, 1 H) 2.90 - 2.97 (m, 1 H) 2.68 - 2.78 (m, 2 H) 2.43 (ddd, *J*=13.87, 10.23, 4.02 Hz, 2 H) 2.00 (br. s., 1 H) 1.75 - 1.90 (m, 3 H) 1.59 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.50 (d, *J*=7.03 Hz, 2 H) 1.44 (dd, *J*=6.02, 2.76 Hz, 7 H) 1.31 - 1.36 (m, 4 H) 1.21 - 1.28 (m, 1 H) 1.05 - 1.19 (m, 3 H) 1.02 (d, *J*=7.03 Hz, 3 H) 0.98 (d, *J*=6.27 Hz, 3 H) 0.92 (s, 3 H) 0.78 - 0.86 (m, 1 H); MS: MS *m/z* 870.8 (M^++1).

Preparation of Compound 4018



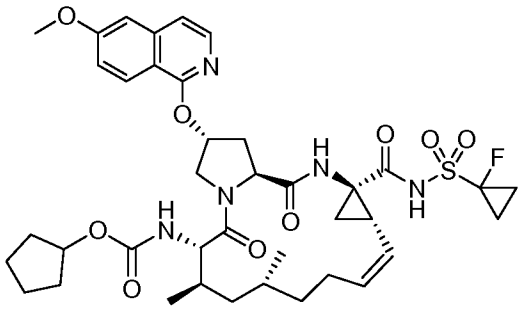
Compound 4018

Compound 4018 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4018: isobutyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.02 (s, 1 H) 8.10 (d, *J*=9.29 Hz, 1 H) 7.92 (d, *J*=5.77 Hz, 1 H) 7.28 (d, *J*=6.02 Hz, 1 H) 7.21 (d, *J*=2.26 Hz, 1 H) 7.11 (dd, *J*=9.16, 2.38 Hz, 1 H) 5.91 (br. s., 1 H) 5.61 (td, *J*=10.16, 6.02 Hz, 1 H) 5.00 (t, *J*=9.91 Hz, 1 H) 4.59 - 4.72 (m, 2 H) 4.04 (dd, *J*=11.42, 3.39 Hz, 1 H) 3.88 - 3.96 (m, 4 H) 3.43 - 3.49 (m, 1 H) 2.71 - 2.79 (m, 2 H) 2.36 - 2.48 (m, 2 H) 1.91 (d, *J*=5.77 Hz, 3 H) 1.72 - 1.81 (m, 3 H) 1.58 - 1.68 (m, 3 H) 1.46 - 1.55 (m, 3 H) 1.21 - 1.31 (m, 2 H) 1.00

(dd, *J*=10.79, 6.78 Hz, 6 H) 0.81 - 0.88 (m, 1 H) 0.78 (dd, *J*=6.78, 1.76 Hz, 6 H); MS: MS *m/z* 772.4 (M^++1).

Preparation of Compound 4019

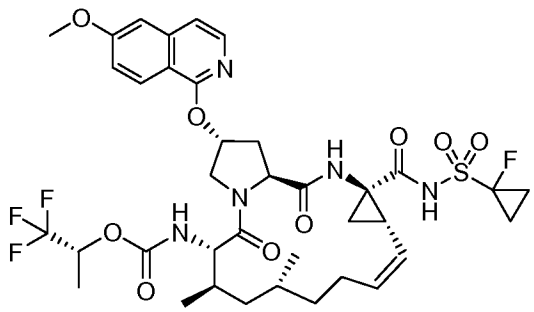


Compound 4019

Compound 4019 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4019: cyclopentyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.02 (s, 1 H) 8.12 (d, *J*=9.03 Hz, 1 H) 7.92 (d, *J*=6.02 Hz, 1 H) 7.29 (d, *J*=6.02 Hz, 1 H) 7.22 (d, *J*=2.26 Hz, 1 H) 7.13 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.91 (br. s., 1 H) 5.61 (td, *J*=10.04, 6.02 Hz, 1 H) 4.99 (t, *J*=9.91 Hz, 1 H) 4.60 - 4.73 (m, 2 H) 4.50 (br. s., 1 H) 4.04 (dd, *J*=11.54, 3.26 Hz, 1 H) 3.89 - 3.97 (m, 4 H) 2.71 - 2.79 (m, 2 H) 2.33 - 2.48 (m, 2 H) 1.84 - 2.05 (m, 2 H) 1.72 - 1.81 (m, 3 H) 1.57 - 1.70 (m, 4 H) 1.40 - 1.55 (m, 9 H) 1.20 - 1.34 (m, 3 H) 0.99 (dd, *J*=14.18, 6.65 Hz, 6 H) 0.79 - 0.87 (m, 1 H); MS: MS *m/z* 784.4 (M^++1).

Preparation of Compound 4020

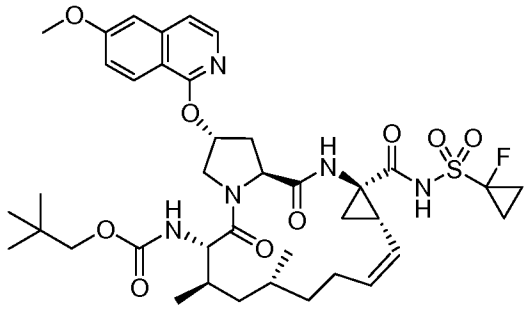


Compound 4020

Compound 4020 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4020: (R)-1,1,1-trifluoropropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.01 (s, 1 H) 8.09 (s, 1 H) 7.89 - 7.93 (m, 1 H) 7.28 (d, *J*=5.77 Hz, 1 H) 7.21 (d, *J*=2.51 Hz, 1 H) 7.08 (dd, *J*=9.16, 2.38 Hz, 1 H) 5.89 (br. s., 1 H) 5.61 (td, *J*=9.85, 6.15 Hz, 1 H) 4.96 - 5.03 (m, 1 H) 4.77 (s, 1 H) 4.63 (dd, *J*=10.04, 7.28 Hz, 1 H) 4.52 (dt, *J*=13.43, 6.84 Hz, 1 H) 4.02 (dd, *J*=11.42, 3.39 Hz, 1 H) 3.92 - 3.96 (m, 3 H) 3.85 - 3.90 (m, 1 H) 2.69 - 2.79 (m, 2 H) 2.33 - 2.48 (m, 2 H) 1.89 - 2.05 (m, 2 H) 1.70 - 1.83 (m, 3 H) 1.57 - 1.69 (m, 2 H) 1.41 - 1.56 (m, 4 H) 1.30 - 1.37 (m, 2 H) 1.18 - 1.27 (m, 4 H) 1.01 (dd, *J*=8.28, 6.78 Hz, 6 H) 0.81 - 0.88 (m, 1 H); MS: MS *m/z* 810.2 (M^+-1).

Preparation of Compound 4022

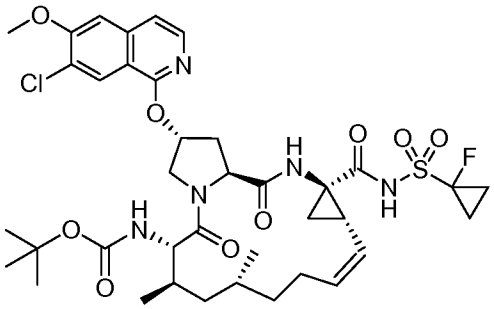


Compound 4022

Compound 4022 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4022: neopentyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.05 (s, 1 H) 8.12 (d, *J*=9.29 Hz, 1 H) 7.93 (d, *J*=6.02 Hz, 1 H) 7.30 (d, *J*=6.02 Hz, 1 H) 7.23 (d, *J*=2.51 Hz, 1 H) 7.12 (dd, *J*=9.16, 2.38 Hz, 1 H) 5.91 (br. s., 1 H) 5.58 - 5.66 (m, 1 H) 5.01 (t, *J*=9.91 Hz, 1 H) 4.74 (d, *J*=11.29 Hz, 1 H) 4.63 (dd, *J*=10.29, 7.28 Hz, 1 H) 4.04 (dd, *J*=11.67, 3.64 Hz, 1 H) 3.95 (s, 3 H) 3.93 (s, 1 H) 3.21 (d, *J*=10.29 Hz, 1 H) 2.72 - 2.79 (m, 2 H) 2.39 - 2.47 (m, 1 H) 1.88 - 2.04 (m, 2 H) 1.74 - 1.81 (m, 3 H) 1.60 - 1.69 (m, 3 H) 1.48 - 1.55 (m, 3 H) 1.26 (br. s., 2 H) 1.01 (d, *J*=3.26 Hz, 6 H) 0.85 (s, 1 H) 0.79 (s, 9 H) 0.70 (br. s., 1 H); MS: MS *m/z* 786.2 (M^++1).

Preparation of Compound 4024

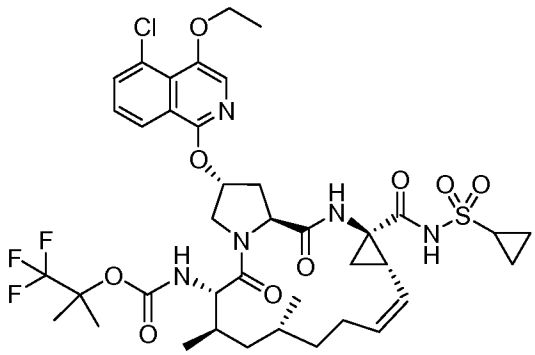


Compound 4024

Compound 4024 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 2024: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-chloro-6-methoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.12 (s, 1 H) 7.96 (d, *J*=6.02 Hz, 1 H) 7.35 (s, 1 H) 7.29 (d, *J*=6.02 Hz, 1 H) 6.60 (d, *J*=8.53 Hz, 1 H) 5.92 (br. s., 1 H) 5.55 - 5.61 (m, 1 H) 4.68 (s, 2 H) 4.02 - 4.06 (m, 4 H) 3.83 (d, *J*=10.29 Hz, 1 H) 2.69 - 2.75 (m, 1 H) 2.35 - 2.51 (m, 2 H) 2.01 (s, 2 H) 1.79 - 1.89 (m, 2 H) 1.73 - 1.76 (m, 1 H) 1.60 (dd, *J*=9.66, 5.40 Hz, 2 H) 1.40 - 1.52 (m, 3 H) 1.23 - 1.32 (m, 2 H) 1.15 (br. s., 1 H) 1.08 (s, 9 H) 1.00 (dd, *J*=14.05, 6.78 Hz, 6 H) 0.81 (t, *J*=12.17 Hz, 1 H); MS: MS *m/z* 804.2 (M^+-1).

Preparation of Compound 4025

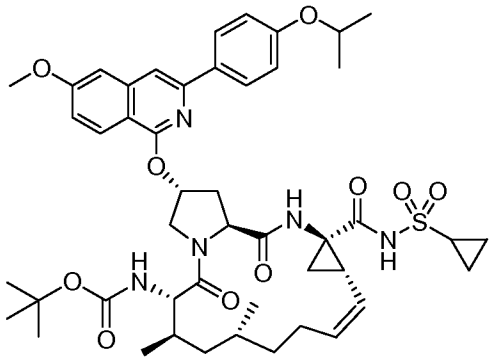


Compound 4025

Compound 4025 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 2025: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(5-chloro-4-ethoxyisoquinolin-1-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.18 (dd, *J*=8.41, 1.13 Hz, 1 H) 7.78 (dd, *J*=7.65, 1.13 Hz, 1 H) 7.71 (s, 1 H) 7.47 (t, *J*=8.03 Hz, 1 H) 5.83 (br. s., 1 H) 5.59 - 5.66 (m, 1 H) 5.06 (t, *J*=9.41 Hz, 1 H) 4.78 (d, *J*=11.80 Hz, 1 H) 4.65 (dd, *J*=10.54, 7.03 Hz, 1 H) 4.18 (q, *J*=6.86 Hz, 2 H) 3.98 (dd, *J*=11.42, 3.14 Hz, 1 H) 3.72 - 3.81 (m, 2 H) 3.26 (d, *J*=7.28 Hz, 1 H) 2.91 - 2.98 (m, 1 H) 2.68 - 2.78 (m, 2 H) 2.40 - 2.47 (m, 2 H) 1.91 - 2.02 (m, 1 H) 1.76 - 1.88 (m, 3 H) 1.60 (d, *J*=4.02 Hz, 1 H) 1.51 - 1.55 (m, 3 H) 1.44 - 1.50 (m, 1 H) 1.40 (d, *J*=5.52 Hz, 3 H) 1.35 (s, 2 H) 1.24 (d, *J*=9.03 Hz, 1 H) 1.14 - 1.18 (m, 1 H) 0.98 - 1.04 (m, 6 H) 0.94 (s, 3 H) 0.83 (t, *J*=11.92 Hz, 1 H); MS: MS *m/z* 855.4 (M^+-1).

Preparation of Compound 4026

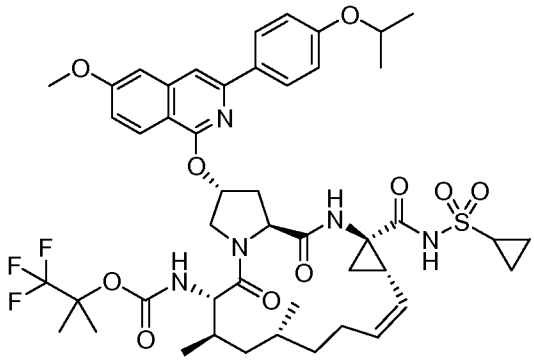


Compound 4026

Compound 4026 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4026: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.05 - 8.13 (m, 3 H) 7.68 (s, 1 H) 7.23 (s, 1 H) 7.02 (d, *J*=8.78 Hz, 3 H) 6.08 (br. s., 1 H) 5.59 - 5.66 (m, 1 H) 5.05 (t, *J*=10.16 Hz, 1 H) 4.55 - 4.74 (m, 3 H) 4.15 (d, *J*=8.53 Hz, 1 H) 3.95 (s, 3 H) 2.94 (br. s., 1 H) 2.72 - 2.85 (m, 2 H) 2.41 - 2.54 (m, 2 H) 2.00 (br. s., 1 H) 1.76 - 1.92 (m, 4 H) 1.60 (d, *J*=9.54 Hz, 1 H) 1.44 - 1.55 (m, 3 H) 1.37 (s, 4 H) 1.31 (br. s., 3 H) 1.23 (s, 6 H) 1.08 - 1.17 (m, 2 H) 1.02 (dd, *J*=16.19, 6.40 Hz, 9 H) 0.83 - 0.93 (m, 2 H); MS: MS *m/z* 886.9 (M^+-1).

Preparation of Compound 4027

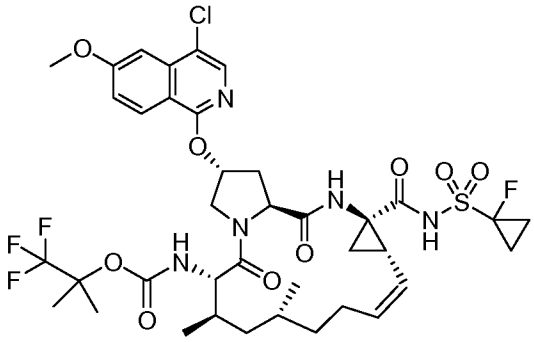


Compound 4027

Compound 4027 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4027: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.05 - 8.13 (m, 3 H) 7.69 (s, 1 H) 7.22 - 7.32 (m, 1 H) 6.99 - 7.06 (m, 3 H) 6.07 (br. s., 1 H) 5.64 (td, *J*=10.04, 5.52 Hz, 1 H) 5.03 - 5.09 (m, 1 H) 4.78 (d, *J*=11.04 Hz, 1 H) 4.64 - 4.74 (m, 2 H) 4.12 (dd, *J*=11.54, 3.51 Hz, 1 H) 3.96 (s, 3 H) 3.87 - 3.92 (m, 1 H) 2.91 - 2.98 (m, 1 H) 2.70 - 2.84 (m, 2 H) 2.38 - 2.53 (m, 2 H) 1.77 - 2.03 (m, 4 H) 1.58 - 1.62 (m, 1 H) 1.45 - 1.55 (m, 2 H) 1.41 - 1.43 (m, 3 H) 1.37 (s, 4 H) 1.30 - 1.35 (m, 2 H) 1.26 (dd, *J*=8.91, 4.64 Hz, 1 H) 1.13 (s, 3 H) 1.04 (d, *J*=7.03 Hz, 3 H) 1.00 (s, 6 H) 0.83 - 0.89 (m, 2 H); MS: MS *m/z* 940.2 (M^+-1).

Preparation of Compound 4028

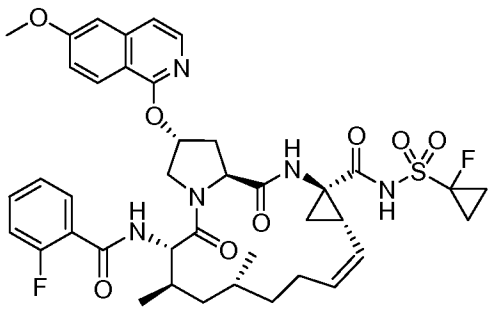


Compound 4028

Compound 4028 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4028: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-chloro-6-methoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.12 - 8.18 (m, 1 H) 8.02 - 8.06 (m, 1 H) 7.40 - 7.43 (m, 1 H) 7.20 - 7.24 (m, 1 H) 5.83 - 5.87 (m, 1 H) 5.56 - 5.63 (m, 1 H) 4.72 - 4.78 (m, 1 H) 4.62 - 4.67 (m, 1 H) 4.00 (s, 4 H) 3.78 - 3.83 (m, 1 H) 2.71 - 2.77 (m, 1 H) 2.35 - 2.49 (m, 2 H) 1.94 - 2.02 (m, 1 H) 1.71 - 1.89 (m, 4 H) 1.56 - 1.67 (m, 3 H) 1.40 - 1.51 (m, 4 H) 1.33 - 1.36 (m, 3 H) 1.30 - 1.32 (m, 1 H) 1.20 - 1.27 (m, 1 H) 1.06 - 1.16 (m, 1 H) 0.95 - 1.03 (m, 6 H) 0.89 - 0.92 (m, 1 H) 0.78 - 0.86 (m, 2 H); MS: MS *m/z* 858.2 (M^+-1).

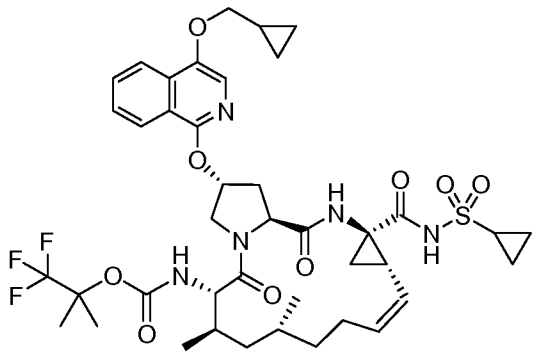
Preparation of Compound 4029



Compound 4029

To a solution *(2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(1-fluorocyclopropylsulfonyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride* (30 mg, 0.044 mmol) in DCM (10 ml) was added 2-fluorobenzoic acid (6.2 mg, 0.044 mmol) followed by HATU (15 mg, 0.05 mmol) and DIPEA (13 mg, 0.1 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The reaction mass was diluted with water and extracted with DCM and washed with brine solution. The combine organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC to get desired compound (14 mg, 40%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.05 (s, 1 H) 8.21 - 8.28 (m, 1 H) 8.09 (d, *J*=9.04 Hz, 1 H) 7.93 (d, *J*=5.77 Hz, 1 H) 7.46 - 7.54 (m, 1 H) 7.11 - 7.29 (m, 4 H) 7.01 - 7.07 (m, 1 H) 5.91 - 5.97 (m, 1 H) 5.63 (d, *J*=6.02 Hz, 1 H) 4.99 - 5.06 (m, 1 H) 4.80 (d, *J*=12.55 Hz, 1 H) 4.64 (dd, *J*=9.91, 6.90 Hz, 1 H) 4.43 - 4.50 (m, 1 H) 4.13 (dd, *J*=11.42, 3.64 Hz, 1 H) 3.94 (s, 3 H) 2.71 - 2.83 (m, 3 H) 2.38 - 2.50 (m, 2 H) 1.97 - 2.12 (m, 2 H) 1.83 - 1.91 (m, 1 H) 1.72 - 1.80 (m, 2 H) 1.43 - 1.70 (m, 5 H) 1.22 - 1.41 (m, 3 H) 1.06 (dd, *J*=10.16, 6.65 Hz, 3 H) 0.90 - 0.96 (m, 1 H); MS: MS *m/z* 794.2 (M^++1).

Preparation of Compound 4030

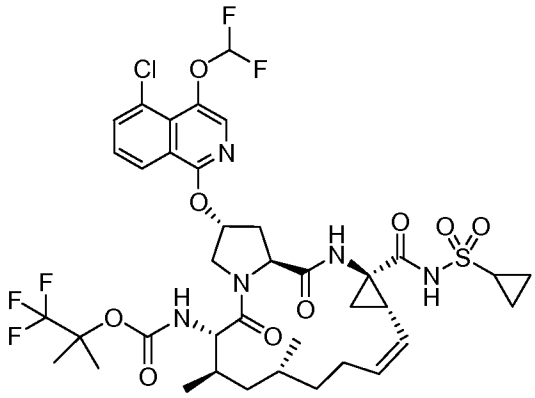


Compound 4030

Compound 4030 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4030: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-(cyclopropylmethoxy)isoquinolin-1-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17 (dd, *J*=8.28, 4.52 Hz, 2 H) 7.75 (td, *J*=7.72, 1.13 Hz, 1 H) 7.54 - 7.59 (m, 2 H) 5.83 (br. s., 1 H) 5.59 - 5.67 (m, 1 H) 5.04 (t, *J*=9.91 Hz, 1 H) 4.76 (d, *J*=11.54 Hz, 1 H) 4.64 - 4.68 (m, 1 H) 3.98 - 4.05 (m, 3 H) 3.80 - 3.85 (m, 1 H) 2.90 - 2.97 (m, 1 H) 2.69 - 2.77 (m, 2 H) 2.43 (ddd, *J*=13.80, 10.04, 4.02 Hz, 2 H) 1.76 - 2.03 (m, 4 H) 1.60 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.44 - 1.55 (m, 2 H) 1.30 - 1.43 (m, 6 H) 1.06 - 1.26 (m, 3 H) 0.95 - 1.04 (m, 9 H) 0.83 (t, *J*=11.80 Hz, 1 H) 0.67 - 0.72 (m, 2 H) 0.43 - 0.47 (m, 2 H); MS: MS *m/z* 846.7(M^+-1).

Preparation of Compound 4031

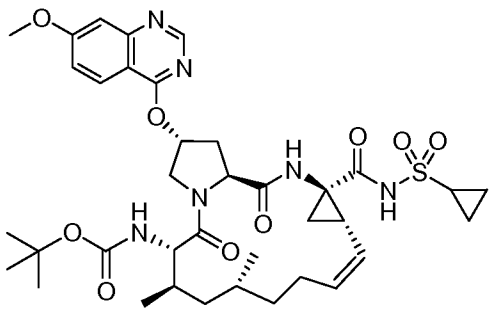


Compound 4031

Compound 4031 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4031: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(5-chloro-4-(difluoromethoxy)isoquinolin-1-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.26 (dd, *J*=8.41, 1.13 Hz, 1 H) 8.01 (s, 1 H) 7.89 (dd, *J*=7.53, 1.00 Hz, 1 H) 7.56 (t, *J*=7.91 Hz, 1 H) 6.84 (s, 1 H) 5.88 - 5.92 (m, 1 H) 5.63 (td, *J*=10.48, 5.65 Hz, 1 H) 5.04 (t, *J*=9.91 Hz, 1 H) 4.67 (dd, *J*=10.29, 7.03 Hz, 1 H) 4.57 (br. s., 1 H) 4.01 (dd, *J*=11.54, 3.26 Hz, 1 H) 3.78 (dd, *J*=10.79, 7.78 Hz, 1 H) 2.91 - 2.97 (m, 1 H) 2.68 - 2.79 (m, 2 H) 2.39 - 2.49 (m, 2 H) 1.75 - 1.90 (m, 3 H) 1.60 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.42 - 1.54 (m, 2 H) 1.30 - 1.36 (m, 6 H) 1.06 - 1.28 (m, 3 H) 1.00 (dd, *J*=15.18, 6.65 Hz, 6 H) 0.93 (s, 3 H) 0.79 - 0.86 (m, 1 H); MS: MS *m/z* 876.2 (M^+-1).

Preparation of Compound 4032

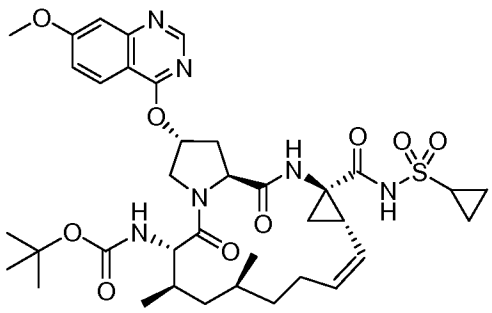


Compound 4032

Compound 4032 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4032: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-methoxyquinazolin-4-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.02 (s, 1 H) 8.86 (s, 1 H) 8.15 (d, *J*=10.04 Hz, 1 H) 7.24 - 7.31 (m, 2 H) 6.04 (br. s., 1 H) 5.64 (td, *J*=10.16, 5.52 Hz, 1 H) 5.05 (t, *J*=10.04 Hz, 1 H) 4.65 (dd, *J*=10.04, 7.28 Hz, 1 H) 4.07 (dd, *J*=11.80, 3.26 Hz, 1 H) 4.01 (s, 3 H) 3.79 (d, *J*=10.79 Hz, 1 H) 2.90 - 3.00 (m, 1 H) 2.67 - 2.83 (m, 2 H) 2.39 - 2.55 (m, 2 H) 1.92 - 2.02 (m, 1 H) 1.76 - 1.88 (m, 3 H) 1.57 - 1.63 (m, 2 H) 1.43 - 1.54 (m, 2 H) 1.28 - 1.39 (m, 2 H) 1.12 - 1.27 (m, 3 H) 1.06 - 1.10 (m, 9 H) 1.01 (dd, *J*=13.43, 6.65 Hz, 6 H) 0.84 (t, *J*=12.92 Hz, 1 H); MS: MS *m/z* 756.4 (M^++1).

Preparation of Compound 4033

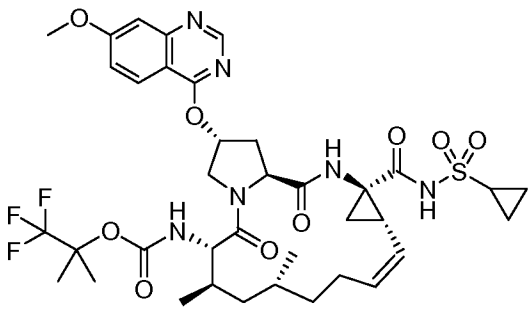


Compound 4033

Compound 4033 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4033: tert-butyl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-methoxyquinazolin-4-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.72 (s, 1 H) 8.11 (d, *J*=9.04 Hz, 1 H) 7.18 - 7.29 (m, 2 H) 6.01 (br. s., 1 H) 5.73 (d, *J*=7.78 Hz, 1 H) 5.02 - 5.16 (m, 1 H) 4.60 - 4.73 (m, 2 H) 4.10 (d, *J*=7.03 Hz, 2 H) 3.98 (s, 3 H) 2.87 - 2.97 (m, 1 H) 2.75 (dd, *J*=13.93, 7.40 Hz, 1 H) 2.49 (d, *J*=9.54 Hz, 2 H) 1.98 (br. s., 2 H) 1.73 (dd, *J*=8.03, 5.52 Hz, 1 H) 1.63 (br. s., 2 H) 1.46 (d, *J*=6.53 Hz, 2 H) 1.21 - 1.35 (m, 4 H) 1.18 (s, 9 H) 1.07 - 1.14 (m, 5 H) 1.02 (br. s., 1 H) 0.94 (d, *J*=6.78 Hz, 3 H); MS: MS *m/z* 756.4 (M^++1).

Preparation of Compound 4034

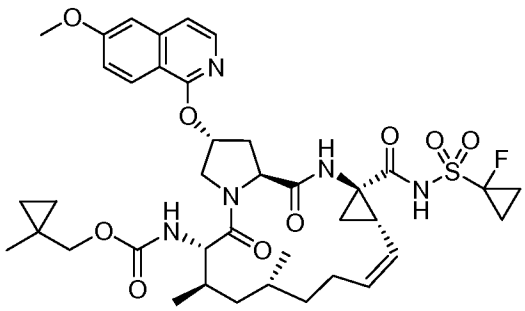


Compound 4034

Compound 4034 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4034: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-methoxyquinazolin-4-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.02 (s, 1 H) 8.78 (s, 1 H) 8.10 (d, *J*=9.03 Hz, 1 H) 7.14 - 7.30 (m, 2 H) 5.97 - 6.01 (m, 1 H) 5.63 (td, *J*=10.16, 5.52 Hz, 1 H) 5.05 (t, *J*=10.04 Hz, 1 H) 4.67 (dd, *J*=10.16, 7.15 Hz, 1 H) 4.02 - 4.07 (m, 1 H) 4.00 (s, 3 H) 3.73 - 3.80 (m, 1 H) 2.89 - 2.99 (m, 1 H) 2.65 - 2.82 (m, 2 H) 2.37 - 2.53 (m, 2 H) 1.73 - 2.03 (m, 5 H) 1.61 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.42 - 1.54 (m, 2 H) 1.28 - 1.33 (m, 4 H) 1.05 - 1.25 (m, 4 H) 0.96 - 1.03 (m, 9 H) 0.79 - 0.88 (m, 1 H); MS: MS *m/z* 807.2 (M^+-1).

Preparation of Compound 4036

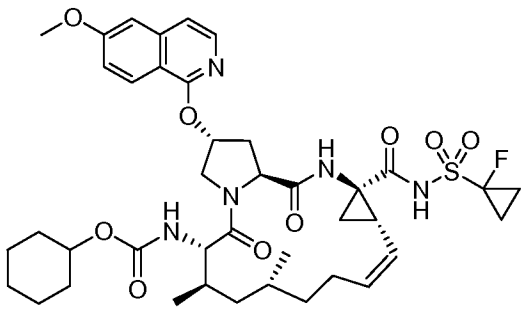


Compound 4036

Compound 4036 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4036: (1-methylcyclopropyl)methyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.10 (d, *J*=9.03 Hz, 1 H) 7.92 (d, *J*=5.77 Hz, 1 H) 7.27 (d, *J*=5.77 Hz, 1 H) 7.21 (d, *J*=2.26 Hz, 1 H) 7.11 (dd, *J*=9.03, 2.51 Hz, 1 H) 7.03 (d, *J*=8.28 Hz, 1 H) 5.91 (br. s., 1 H) 5.62 (td, *J*=10.10, 5.90 Hz, 1 H) 5.01 (t, *J*=9.91 Hz, 1 H) 4.58 - 4.73 (m, 2 H) 4.04 (dd, *J*=11.54, 3.51 Hz, 1 H) 3.89 - 3.97 (m, 5 H) 3.47 (s, 1 H) 2.71 - 2.80 (m, 2 H) 2.33 - 2.51 (m, 2 H) 1.86 - 2.07 (m, 2 H) 1.72 - 1.83 (m, 3 H) 1.58 - 1.69 (m, 3 H) 1.45 - 1.56 (m, 4 H) 1.20 - 1.33 (m, 2 H) 0.96 - 1.06 (m, 7 H) 0.81 - 0.89 (m, 1 H) 0.15 - 0.35 (m, 4 H); MS: MS *m/z* 784.4 (M^++1).

Preparation of Compound 4037

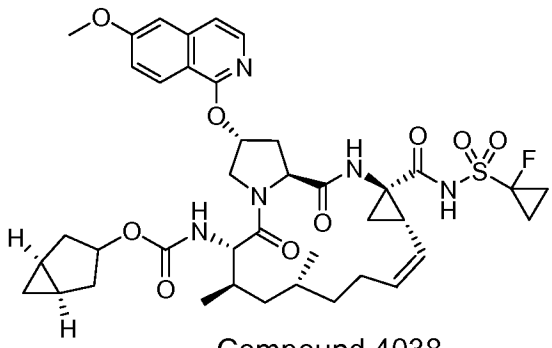


Compound 4037

Compound 4037 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4037: cyclohexyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.03 (s, 1 H) 8.10 (d, *J*=9.29 Hz, 1 H) 7.92 (d, *J*=6.02 Hz, 1 H) 7.29 (d, *J*=6.02 Hz, 1 H) 7.23 (d, *J*=2.51 Hz, 1 H) 7.12 (dd, *J*=9.16, 2.38 Hz, 1 H) 5.90 (br. s., 1 H) 5.61 (td, *J*=10.04, 5.77 Hz, 1 H) 5.00 (t, *J*=9.79 Hz, 1 H) 4.73 (d, *J*=11.54 Hz, 1 H) 4.63 (dd, *J*=10.04, 7.53 Hz, 1 H) 4.04 (dd, *J*=11.17, 3.39 Hz, 2 H) 3.95 (s, 3 H) 3.91 (d, *J*=10.79 Hz, 1 H) 2.69 - 2.79 (m, 2 H) 2.33 - 2.49 (m, 2 H) 2.00 (br. s., 1 H) 1.89 (d, *J*=5.52 Hz, 1 H) 1.71 - 1.81 (m, 3 H) 1.62 - 1.69 (m, 3 H) 1.54 - 1.62 (m, 3 H) 1.45 - 1.54 (m, 4 H) 1.41 (m, 1H) 1.05 - 1.31 (m, 6 H) 1.00 (dd, *J*=12.92, 6.65 Hz, 6 H) 0.76 - 0.89 (m, 1 H); MS: MS *m/z* 798.4 (M^++1).

Preparation of Compound 4038

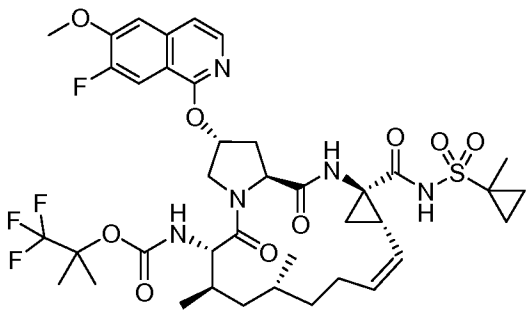


Compound 4038

Compound 4038 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4038: (1R,5S)-bicyclo[3.1.0]hexan-3-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.02 (s, 1 H) 8.11 (d, *J*=9.03 Hz, 1 H) 7.92 (d, *J*=6.02 Hz, 1 H) 7.31 (d, *J*=6.02 Hz, 1 H) 7.24 (d, *J*=2.51 Hz, 1 H) 7.16 (dd, *J*=9.16, 2.38 Hz, 1 H) 5.91 (br. s., 1 H) 5.62 (td, *J*=10.04, 6.02 Hz, 1 H) 4.95 - 5.04 (m, 1 H) 4.52 - 4.72 (m, 3 H) 4.04 (dd, *J*=11.54, 3.26 Hz, 1 H) 3.96 (s, 3 H) 3.90 (d, *J*=11.04 Hz, 1 H) 2.69 - 2.79 (m, 2 H) 2.32 - 2.49 (m, 2 H) 1.94 - 2.05 (m, 2 H) 1.86 - 1.92 (m, 1 H) 1.76 (td, *J*=8.78, 5.52 Hz, 4 H) 1.56 - 1.71 (m, 3 H) 1.45 - 1.55 (m, 3 H) 1.41 - 1.45 (m, 1 H) 1.29 - 1.39 (m, 2 H) 1.19 - 1.27 (m, 1 H) 1.14 (d, *J*=3.26 Hz, 1 H) 0.99 (dd, *J*=17.32, 6.78 Hz, 6 H) 0.77 - 0.87 (m, 1 H) 0.27 - 0.41 (m, 2 H); MS: MS *m/z* 794.2 (M^+-1).

Preparation of Compound 4039

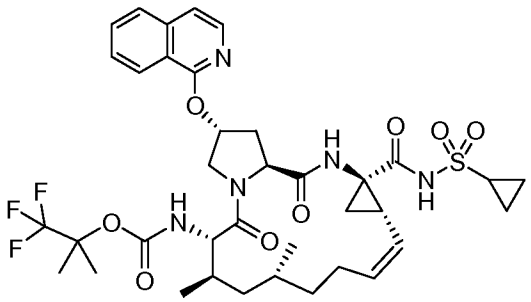


Compound 4039

Compound 4039 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4039: ,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.04 (s, 1 H) 7.96 (s, 1 H) 7.80 (d, *J*=11.54 Hz, 1 H) 7.41 (d, *J*=8.28 Hz, 1 H) 7.31 (d, *J*=5.77 Hz, 1 H) 5.90 (t, *J*=3.26 Hz, 1 H) 5.63 (td, *J*=10.48, 5.90 Hz, 1 H) 5.01 (t, *J*=10.04 Hz, 1 H) 4.64 - 4.74 (m, 2 H) 4.03 (s, 4 H) 3.83 (d, *J*=10.79 Hz, 1 H) 2.66 - 2.79 (m, 2 H) 2.39 - 2.51 (m, 2 H) 1.74 - 2.02 (m, 4 H) 1.62 - 1.70 (m, 1 H) 1.58 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.38 - 1.53 (m, 9 H) 1.25 - 1.30 (m, 1 H) 1.13 (s, 3 H) 1.01 (t, *J*=6.27 Hz, 6 H) 0.85 - 0.93 (m, 3 H); MS: MS *m/z* 838.2 (M^+-1).

Preparation of Compound 4040

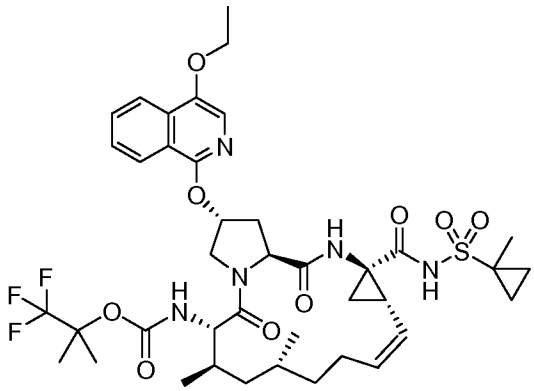


Compound 4040

Compound 4040 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4040: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(isoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 11.18 (br. s., 1 H) 9.00 (br. s., 1 H) 8.13 (d, *J*=8.28 Hz, 1 H) 8.04 (d, *J*=5.77 Hz, 1 H) 7.91 (d, *J*=8.03 Hz, 1 H) 7.73 - 7.83 (m, 1 H) 7.58 (t, *J*=7.53 Hz, 1 H) 7.41 (d, *J*=5.77 Hz, 1 H) 5.84 (br. s., 1 H) 5.48 - 5.59 (m, 1 H) 5.05 (t, *J*=9.91 Hz, 1 H) 4.49 - 4.60 (m, 2 H) 3.91 (dd, *J*=11.42, 3.39 Hz, 1 H) 3.71 (dd, *J*=10.79, 8.03 Hz, 1 H) 2.88 - 2.96 (m, 1 H) 2.62 - 2.73 (m, 2 H) 2.27 - 2.36 (m, 2 H) 1.79 - 1.94 (m, 2 H) 1.66 - 1.73 (m, 1 H) 1.53 - 1.62 (m, 2 H) 1.43 (d, *J*=7.53 Hz, 1 H) 1.37 (br. s., 2 H) 1.33 (s, 3 H) 1.13 (dd, *J*=11.80, 7.28 Hz, 3 H) 1.04 (s, 3 H) 0.89 - 0.99 (m, 6 H) 0.71 - 0.78 (m, 1 H); MS: MS *m/z* 778.2 (M^++1).

Preparation of Compound 4041

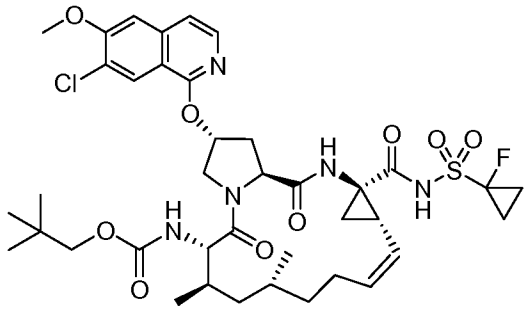


Compound 4041

Compound 4041 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4041: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.15 (t, *J*=7.91 Hz, 2 H) 7.73 (t, *J*=7.65 Hz, 1 H) 7.52 - 7.59 (m, 2 H) 5.83 (br. s., 1 H) 5.58 - 5.66 (m, 1 H) 4.98 (br. s., 1 H) 4.76 (d, *J*=12.55 Hz, 2 H) 4.66 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.57 (s, 1 H) 4.21 - 4.26 (m, 2 H) 4.02 (dd, *J*=11.54, 3.26 Hz, 1 H) 3.83 (d, *J*=10.79 Hz, 1 H) 2.70 - 2.78 (m, 2 H) 2.43 (ddd, *J*=13.74, 9.85, 4.27 Hz, 2 H) 1.97 (br. s., 3 H) 1.73 - 1.83 (m, 2 H) 1.66 (d, *J*=11.04 Hz, 1 H) 1.51 - 1.59 (m, 7 H) 1.37 - 1.51 (m, 4 H) 1.30 - 1.36 (m, 3 H) 1.24 (d, *J*=12.80 Hz, 1 H) 0.93 - 1.04 (m, 6 H) 0.79 - 0.91 (m, 2 H); MS: MS *m/z* 836.4 (M^++1).

Preparation of Compound 4042

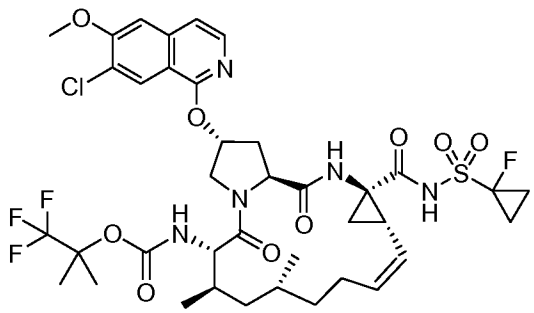


Compound 4042

Compound 4042 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4042: neopentyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-chloro-6-methoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.16 (s, 1 H) 7.96 (d, *J*=6.02 Hz, 1 H) 7.36 (s, 1 H) 7.31 (d, *J*=5.77 Hz, 1 H) 5.93 (br. s., 1 H) 5.61 (br. s., 1 H) 4.74 (d, *J*=11.04 Hz, 2 H) 4.57 - 4.67 (m, 2 H) 4.00 - 4.05 (m, 4 H) 3.88 (d, *J*=10.79 Hz, 1 H) 3.39 (br. s., 1 H) 3.22 (d, *J*=10.54 Hz, 1 H) 2.70 - 2.79 (m, 2 H) 2.36 - 2.49 (m, 2 H) 2.01 (br. s., 1 H) 1.90 (br. s., 1 H) 1.71 - 1.83 (m, 3 H) 1.62 (br. s., 2 H) 1.49 (d, *J*=12.80 Hz, 4 H) 1.01 (t, *J*=6.65 Hz, 6 H) 0.82 - 0.95 (m, 2 H) 0.78 (s, 9 H); MS: MS *m/z* 818.2 (M^+-1).

Preparation of Compound 4043

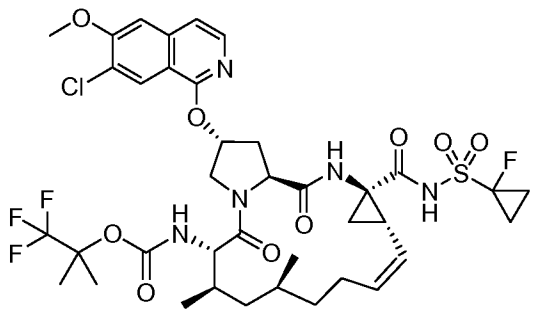


Compound 4043

Compound 4043 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4043: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-chloro-6-methoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.13 (s, 1 H) 7.98 (s, 1 H) 7.37 (s, 1 H) 7.31 (s, 1 H) 5.93 (br. s., 1 H) 5.61 (d, *J*=5.77 Hz, 1 H) 5.01 (br. s., 1 H) 4.68 - 4.76 (m, 2 H) 3.97 - 4.05 (m, 4 H) 3.76 - 3.81 (m, 1 H) 3.28 (br. s., 1 H) 2.71 - 2.78 (m, 2 H) 2.35 - 2.50 (m, 2 H) 2.00 (d, *J*=12.55 Hz, 1 H) 1.83 - 1.92 (m, 1 H) 1.72 - 1.82 (m, 3 H) 1.57 - 1.70 (m, 3 H) 1.40 - 1.56 (m, 4 H) 1.28 - 1.32 (m, 2 H) 1.23 (br. s., 1 H) 0.97 - 1.03 (m, 9 H) 0.79 - 0.87 (m, 1 H); MS: MS *m/z* 860.2 (M^++1).

Preparation of Compound 4044

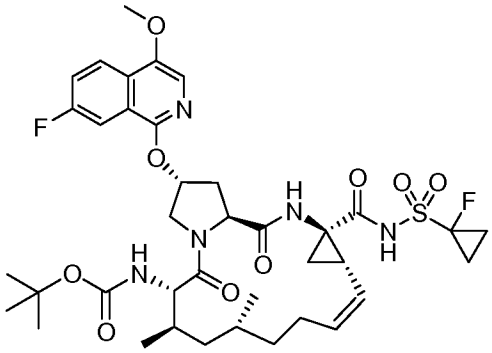


Compound 4044

Compound 4044 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4044: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-(7-chloro-6-methoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.15 (s, 1 H) 7.97 (d, *J*=5.77 Hz, 1 H) 7.36 (s, 1 H) 7.31 (d, *J*=5.77 Hz, 1 H) 5.93 (br. s., 1 H) 5.70 (br. s., 1 H) 5.05 (br. s., 1 H) 4.72 - 4.79 (m, 1 H) 4.55 (d, *J*=11.54 Hz, 1 H) 4.09 (br. s., 1 H) 4.04 (s, 3 H) 2.72 (br. s., 1 H) 2.51 (br. s., 1 H) 2.01 (br. s., 2 H) 1.59 - 1.76 (m, 5 H) 1.42 - 1.55 (m, 6H) 1.40 (s, 3 H) 1.29 - 1.34 (m, 2 H) 1.24 (br. s., 2 H) 1.18 (s, 3 H) 1.13 - 1.16 (m, 1 H) 1.10 (d, *J*=6.78 Hz, 3 H) 0.97 - 1.04 (m, 1 H) 0.94 (d, *J*=6.78 Hz, 3 H); MS: MS *m/z* 858.2(M^+-1).

Preparation of Compound 4045

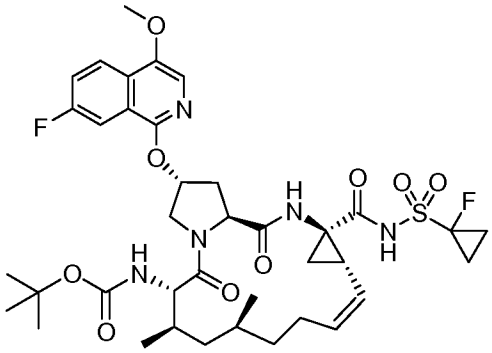


Compound 4045

Compound 4012 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4045: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17 (dd, *J*=9.03, 5.27 Hz, 1 H) 7.75 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.50 - 7.58 (m, 2 H) 6.62 (d, *J*=7.78 Hz, 1 H) 5.84 (br. s., 1 H) 5.54 - 5.63 (m, 1 H) 5.14 (br. s., 1 H) 4.71 (d, *J*=11.29 Hz, 1 H) 4.57 - 4.65 (m, 1 H) 4.01 - 4.06 (m, 4 H) 3.82 - 3.89 (m, 1 H) 2.74 (dd, *J*=14.05, 7.03 Hz, 1 H) 2.32 - 2.49 (m, 2 H) 2.01 (s, 1 H) 1.78 - 1.91 (m, 2 H) 1.69 - 1.77 (m, 2 H) 1.57 - 1.68 (m, 2 H) 1.39 - 1.55 (m, 3 H) 1.20 - 1.36 (m, 2 H) 1.12 (s, 9 H) 1.00 (dd, *J*=11.67, 6.65 Hz, 6 H) 0.82 (t, *J*=11.54 Hz, 1 H); MS: MS *m/z* 790.4(M^++1).

Preparation of Compound 4046

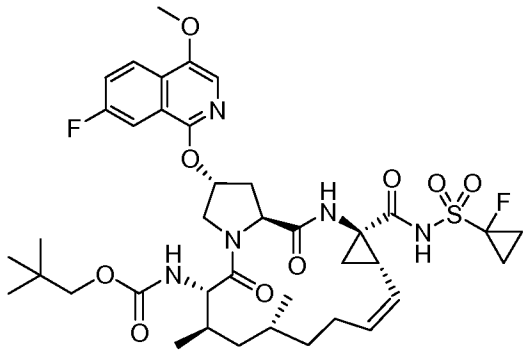


Compound 4046

Compound 4046 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4046: tert-butyl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17 (dd, *J*=9.16, 5.40 Hz, 1 H) 7.73 - 7.78 (m, 1 H) 7.50 - 7.58 (m, 2 H) 5.86 (br. s., 1 H) 5.72 (d, *J*=9.54 Hz, 1 H) 5.07 (br. s., 1 H) 4.65 - 4.74 (m, 1 H) 4.52 (d, *J*=11.54 Hz, 1 H) 4.06 - 4.17 (m, 2 H) 4.03 (s, 3 H) 2.72 (dd, *J*=13.93, 7.15 Hz, 1 H) 2.56 - 2.67 (m, 1 H) 2.41 - 2.55 (m, 2 H) 1.91 - 2.04 (m, 2 H) 1.71 (dd, *J*=8.16, 5.65 Hz, 2 H) 1.65 (dd, *J*=10.79, 5.77 Hz, 3 H) 1.39 - 1.54 (m, 3 H) 1.29 (d, *J*=17.82 Hz, 3 H) 1.21 (s, 9 H) 1.10 (d, *J*=6.78 Hz, 3 H) 0.93 (d, *J*=6.78 Hz, 3 H); MS: MS *m/z* 790.4(M^++1).

Preparation of Compound 4047

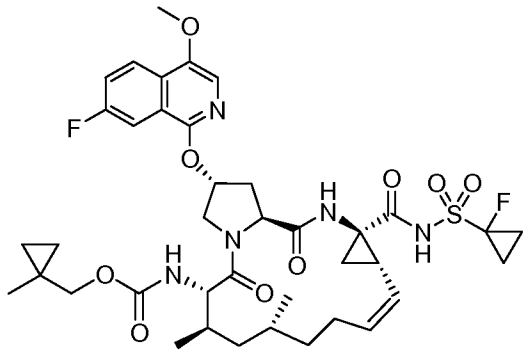


Compound 4047

Compound 4047 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4047: neopentyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.18 (dd, *J*=9.16, 5.14 Hz, 1 H) 7.82 (dd, *J*=9.66, 2.38 Hz, 1 H) 7.50 - 7.58 (m, 1 H) 7.07 (d, *J*=7.78 Hz, 1 H) 5.84 (br. s., 1 H) 5.61 (d, *J*=5.27 Hz, 1 H) 4.73 (d, *J*=11.80 Hz, 2 H) 4.56 - 4.63 (m, 1 H) 4.04 (s, 3 H) 4.01 (br. s., 1 H) 3.92 (d, *J*=10.54 Hz, 1 H) 3.44 - 3.48 (m, 1 H) 2.70 - 2.79 (m, 2 H) 2.36 - 2.48 (m, 2 H) 2.01 (s, 1 H) 1.85 - 1.96 (m, 1 H) 1.70 - 1.85 (m, 3 H) 1.57 - 1.69 (m, 2 H) 1.49 (d, *J*=16.81 Hz, 3 H) 1.19 - 1.38 (m, 1 H) 0.98 - 1.06 (m, 6 H) 0.84 - 0.93 (m, 2 H) 0.81 (s, 9 H) 0.72 (br. s., 1 H); MS: MS *m/z* 804.4 (M^++1).

Preparation of Compound 4048

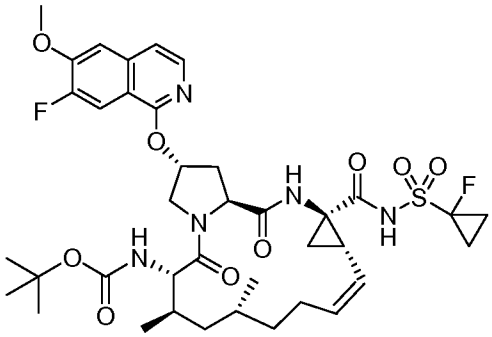


Compound 4048

Compound 4048 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4048: (1-methylcyclopropyl)methyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.37 (dd, *J*=9.04, 5.52 Hz, 1 H) 7.00 (dd, *J*=9.54, 2.51 Hz, 1 H) 6.69 - 6.77 (m, 2 H) 6.25 (d, *J*=8.53 Hz, 1 H) 5.03 (br. s., 1 H) 4.76 - 4.85 (m, 1 H) 4.21 (br. s., 1 H) 3.91 (d, *J*=11.04 Hz, 1 H) 3.80 (dd, *J*=9.91, 7.40 Hz, 1 H) 3.18 - 3.24 (m, 4 H) 3.11 (dd, *J*=10.54, 8.53 Hz, 1 H) 2.71 - 2.75 (m, 1 H) 2.60 - 2.64 (m, 1 H) 1.87 - 1.99 (m, 2 H) 1.54 - 1.67 (m, 2 H) 1.05 - 1.24 (m, 2 H) 0.90 - 1.03 (m, 2 H) 0.77 - 0.88 (m, 2 H) 0.60 - 0.75 (m, 3 H) 0.42 - 0.58 (m, 2 H) 0.17 - 0.24 (m, 9 H) 0.00 - 0.08 (m, 1 H) -0.63 - -0.45 (m, 4 H); MS: MS *m/z* 800.2 (M^+-1).

Preparation of Compound 4049

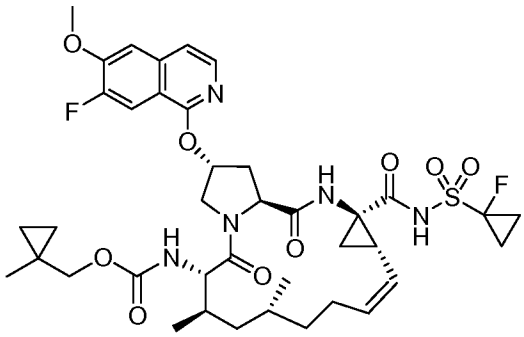


Compound 4049

Compound 4049 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4049: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.94 (d, *J*=6.02 Hz, 1 H) 7.79 (s, 1 H) 7.39 (d, *J*=8.28 Hz, 1 H) 7.30 (d, *J*=6.02 Hz, 1 H) 5.91 (br. s., 1 H) 5.57 - 5.65 (m, 1 H) 5.01 (br. s., 1 H) 4.71 (d, *J*=11.04 Hz, 1 H) 4.63 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.00 - 4.06 (m, 4 H) 3.86 (d, *J*=10.79 Hz, 1 H) 2.70 - 2.80 (m, 2 H) 2.36 - 2.49 (m, 2 H) 1.93 - 2.06 (m, 1 H) 1.71 - 1.91 (m, 3 H) 1.58 - 1.69 (m, 2 H) 1.44 - 1.57 (m, 4 H) 1.22 - 1.34 (m, 2 H) 1.16 (s, 9 H) 1.01 (dd, *J*=8.78, 6.78 Hz, 6 H) 0.80 - 0.87 (m, 1 H); MS: MS *m/z* 790.2 (M^++1).

Preparation of Compound 4050

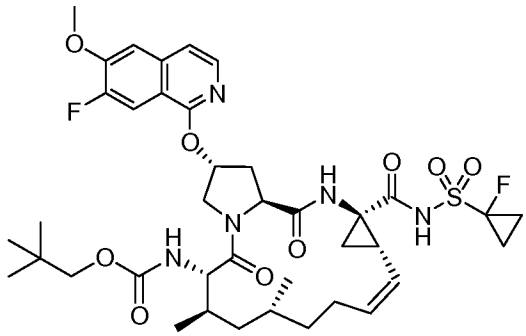


Compound 4050

Compound 4050 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4050: (1-methylcyclopropyl)methyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.03 (s, 1 H) 7.94 (d, *J*=6.02 Hz, 1 H) 7.86 (d, *J*=11.54 Hz, 1 H) 7.40 (d, *J*=8.28 Hz, 1 H) 7.31 (d, *J*=5.77 Hz, 1 H) 5.89 (br. s., 1 H) 5.56 - 5.67 (m, 1 H) 4.97 - 5.05 (m, 1 H) 4.74 (d, *J*=11.29 Hz, 1 H) 4.57 - 4.64 (m, 1 H) 4.00 - 4.06 (m, 4 H) 3.91 (d, *J*=10.79 Hz, 1 H) 3.56 (s, 1 H) 3.45 (d, *J*=11.04 Hz, 1 H) 2.69 - 2.81 (m, 2 H) 2.33 - 2.48 (m, 2 H) 1.86 - 2.04 (m, 2 H) 1.71 - 1.85 (m, 3 H) 1.56 - 1.70 (m, 2 H) 1.40 - 1.55 (m, 3 H) 1.18 - 1.40 (m, 2 H) 0.97 - 1.05 (m, 9 H) 0.86 (t, *J*=11.92 Hz, 1 H) 0.18 - 0.37 (m, 4 H); MS: MS *m/z* 802.2(M^++1).

Preparation of Compound 4051

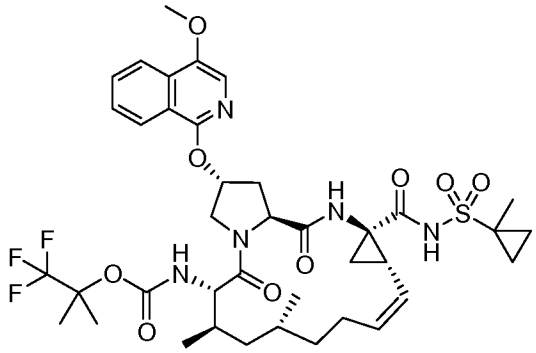


Compound 4051

Compound 4051 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4051: neopentyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.94 (d, *J*=6.02 Hz, 1 H) 7.87 (s, 1 H) 7.39 (d, *J*=8.28 Hz, 1 H) 7.30 (d, *J*=6.02 Hz, 1 H) 5.88 (br. s., 1 H) 5.58 (d, *J*=6.02 Hz, 1 H) 4.73 (d, *J*=12.05 Hz, 1 H) 4.54 - 4.64 (m, 1 H) 4.00 - 4.05 (m, 4 H) 3.89 - 3.96 (m, 1 H) 3.45 - 3.49 (m, 1 H) 3.37 (s, 1 H) 2.76 (dd, *J*=13.55, 6.78 Hz, 1 H) 2.64 (br. s., 1 H) 2.34 - 2.52 (m, 2 H) 1.86 - 2.04 (m, 2 H) 1.77 - 1.85 (m, 1 H) 1.73 (dd, *J*=7.78, 5.52 Hz, 2 H) 1.55 - 1.67 (m, 2 H) 1.44 (d, *J*=14.31 Hz, 3 H) 1.22 - 1.36 (m, 2 H) 0.98 - 1.05 (m, 6 H) 0.87 (br. s., 1 H) 0.83 (s, 9 H) 0.73 (br. s., 1 H); MS: MS *m/z* 802.2(M^+-1).

Preparation of Compound 4052

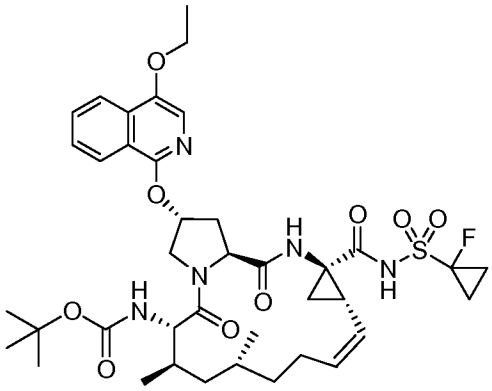


Compound 4052

Compound 4052 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4052: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.14 (dd, *J*=17.07, 8.28 Hz, 2 H) 7.74 (t, *J*=7.28 Hz, 1 H) 7.52 - 7.60 (m, 2 H) 5.84 (br. s., 1 H) 5.57 - 5.67 (m, 1 H) 5.01 (t, *J*=9.66 Hz, 1 H) 4.76 (d, *J*=11.54 Hz, 1 H) 4.66 (dd, *J*=10.29, 7.03 Hz, 1 H) 3.99 - 4.05 (m, 4 H) 3.82 (s, 1 H) 2.69 - 2.79 (m, 2 H) 2.39 - 2.49 (m, 2 H) 1.98 (br. s., 1 H) 1.88 (d, *J*=5.77 Hz, 1 H) 1.72 - 1.82 (m, 2 H) 1.62 - 1.69 (m, 1 H) 1.57 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.53 (s, 3 H) 1.39 - 1.51 (m, 3 H) 1.35 (s, 3 H) 1.21 - 1.31 (m, 1 H) 0.94 - 1.04 (m, 9 H) 0.79 - 0.93 (m, 3 H); MS: MS *m/z* 820.2 (M^+-1).

Preparation of Compound 4053

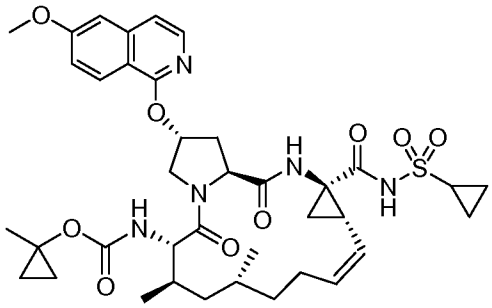


Compound 4053

Compound 4053 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4053: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.03 (s, 1 H) 8.15 (dd, *J*=15.69, 8.41 Hz, 2 H) 7.72 (t, *J*=7.28 Hz, 1 H) 7.50 - 7.58 (m, 2 H) 5.84 (br. s., 1 H) 5.61 (td, *J*=10.16, 6.02 Hz, 1 H) 4.99 (t, *J*=9.91 Hz, 1 H) 4.73 (d, *J*=11.04 Hz, 1 H) 4.62 (dd, *J*=10.16, 7.15 Hz, 1 H) 4.23 (q, *J*=6.86 Hz, 2 H) 4.04 (dd, *J*=11.42, 3.39 Hz, 1 H) 3.88 (d, *J*=10.79 Hz, 1 H) 2.71 - 2.79 (m, 2 H) 2.34 - 2.48 (m, 2 H) 1.93 - 2.03 (m, 1 H) 1.72 - 1.91 (m, 4 H) 1.57 - 1.70 (m, 2 H) 1.51 - 1.56 (m, 4 H) 1.39 - 1.50 (m, 3 H) 1.22 - 1.32 (m, 1 H) 1.13 (s, 9 H) 1.00 (dd, *J*=11.92, 6.65 Hz, 6 H) 0.78 - 0.86 (m, 1 H); MS: MS *m/z* 784.2 (M^+-1).

Preparation of Compound 4054

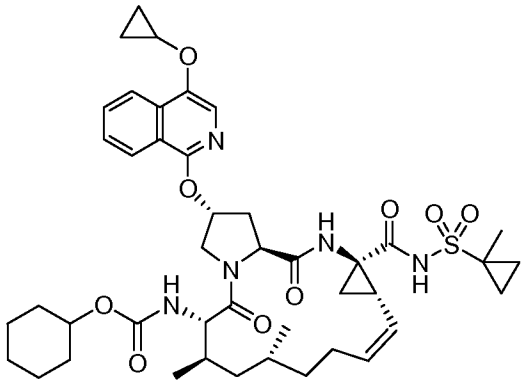


Compound 4054

Compound 4054 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4054: 1-methylcyclopropyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.95 - 9.00 (m, 1 H) 8.09 - 8.18 (m, 1 H) 7.93 - 8.01 (m, 1 H) 7.34 - 7.39 (m, 1 H) 7.27 - 7.33 (m, 1 H) 5.93 - 6.01 (m, 1 H) 5.59 - 5.75 (m, 1 H) 5.06 - 5.13 (m, 1 H) 4.57 - 4.71 (m, 2 H) 4.00 - 4.10 (m, 4 H) 3.90 - 3.96 (m, 1 H) 2.87 - 2.98 (m, 1 H) 2.68 - 2.76 (m, 1 H) 2.56 - 2.66 (m, 2 H) 2.45 - 2.54 (m, 1 H) 1.92 - 2.03 (m, 1 H) 1.79 - 1.90 (m, 1 H) 1.72 - 1.78 (m, 1 H) 1.53 - 1.70 (m, 3 H) 1.27 - 1.47 (m, 5 H) 1.00 - 1.18 (m, 8 H) 0.89 - 0.98 (m, 3 H) 0.58 - 0.66 (m, 1 H) 0.44 - 0.51 (m, 1 H) 0.36 - 0.42 (m, 1 H) 0.27 - 0.32 (m, 1 H); MS: MS *m/z* 753.2 (M^++1).

Preparation of Compound 4055

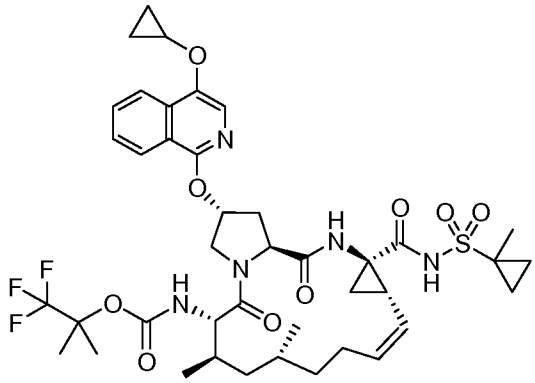


Compound 4055

Compound 4055 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4055: cyclohexyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-cyclopropoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.15 (d, *J*=8.03 Hz, 1 H) 8.04 (d, *J*=8.53 Hz, 1 H) 7.89 (s, 1 H) 7.72 (t, *J*=7.78 Hz, 1 H) 7.53 - 7.58 (m, 1 H) 6.89 (d, *J*=8.28 Hz, 1 H) 5.87 (br. s., 1 H) 5.59 - 5.67 (m, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.73 (d, *J*=12.05 Hz, 1 H) 4.65 (dd, *J*=9.91, 7.40 Hz, 1 H) 4.01 (d, *J*=3.26 Hz, 3 H) 3.91 (br. s., 1 H) 3.07 (q, *J*=7.78 Hz, 1 H) 2.71 - 2.79 (m, 2 H) 2.40 - 2.48 (m, 1 H) 2.00 (br. s., 1 H) 1.89 (br. s., 1 H) 1.77 (dd, *J*=8.28, 5.77 Hz, 2 H) 1.63 - 1.71 (m, 3 H) 1.56 - 1.60 (m, 1 H) 1.53 (s, 3 H) 1.49 (d, *J*=4.02 Hz, 1 H) 1.43 - 1.46 (m, 1 H) 1.38 - 1.43 (m, 2 H) 1.30 - 1.34 (m, 4 H) 1.23 (d, *J*=8.53 Hz, 2 H) 1.13 (br. s., 2 H) 1.00 (dd, *J*=14.93, 6.65 Hz, 6 H) 0.89 - 0.94 (m, 4 H) 0.86 (d, *J*=2.76 Hz, 3 H); MS: MS *m/z* 821.4 (M^++1).

Preparation of Compound 4056

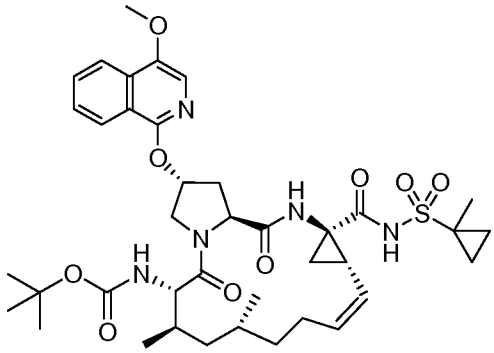


Compound 4056

Compound 4056 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4056: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-cyclopropoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.16 (d, *J*=8.28 Hz, 1 H) 8.03 (d, *J*=8.28 Hz, 1 H) 7.89 (s, 1 H) 7.72 (td, *J*=7.65, 1.25 Hz, 1 H) 7.53 - 7.58 (m, 1 H) 7.28 (d, *J*=8.03 Hz, 1 H) 5.84 (br. s., 1 H) 5.59 - 5.66 (m, 1 H) 5.01 (t, *J*=9.91 Hz, 1 H) 4.78 (d, *J*=12.05 Hz, 1 H) 4.67 (dd, *J*=10.29, 7.03 Hz, 1 H) 3.97 - 4.05 (m, 2 H) 3.80 - 3.86 (m, 1 H) 2.70 - 2.78 (m, 2 H) 2.40 - 2.48 (m, 2 H) 1.98 (br. s., 1 H) 1.83 - 1.92 (m, 1 H) 1.77 (dd, *J*=8.28, 5.52 Hz, 2 H) 1.66 (dd, *J*=9.66, 4.64 Hz, 1 H) 1.54 - 1.59 (m, 1 H) 1.53 (s, 3 H) 1.41 - 1.49 (m, 2 H) 1.34 (s, 3 H) 1.31 (br. s., 1 H) 1.21 - 1.29 (m, 1 H) 1.00 (dd, *J*=12.05, 6.78 Hz, 6 H) 0.88 - 0.93 (m, 7 H) 0.79 - 0.88 (m, 3 H); MS: MS *m/z* 847.2(M^+-1).

Preparation of Compound 4057

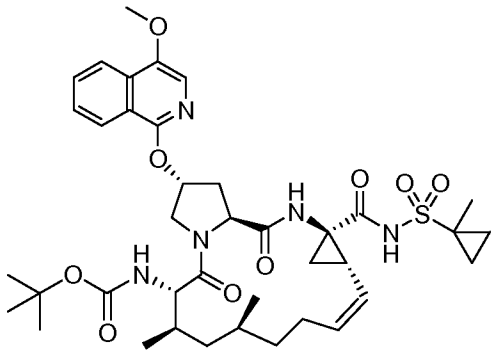


Compound 4057

Compound 4057 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4057: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.04 (s, 1 H) 8.08 - 8.20 (m, 2 H) 7.73 (t, *J*=8.03 Hz, 1 H) 7.52 - 7.60 (m, 2 H) 5.85 (br. s., 1 H) 5.63 (td, *J*=10.16, 6.02 Hz, 1 H) 5.01 (t, *J*=10.04 Hz, 1 H) 4.73 (d, *J*=11.04 Hz, 1 H) 4.63 (dd, *J*=9.91, 6.90 Hz, 1 H) 4.00 - 4.09 (m, 4 H) 3.89 (d, *J*=11.04 Hz, 1 H) 2.70 - 2.80 (m, 2 H) 2.38 - 2.49 (m, 2 H) 1.92 - 2.03 (m, 1 H) 1.74 - 1.91 (m, 3 H) 1.61 - 1.70 (m, 1 H) 1.40 - 1.59 (m, 6 H) 1.20 - 1.38 (m, 2 H) 1.14 (s, 9 H) 1.01 (dd, *J*=10.67, 6.65 Hz, 6 H) 0.79 - 0.94 (m, 3 H); MS: MS *m/z* 768.4 (M^++1).

Preparation of Compound 4058

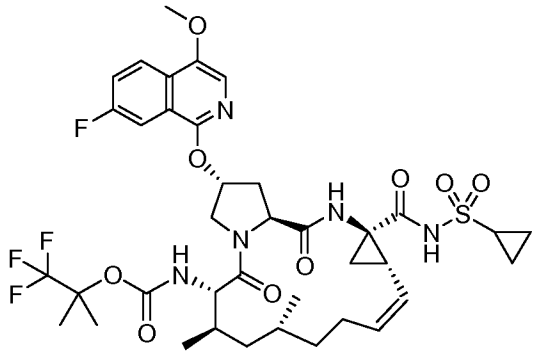


Compound 4058

Compound 4058 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4058: tert-butyl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-(4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.09 (s, 1 H) 8.19 (d, *J*=8.53 Hz, 1 H) 8.12 (d, *J*=8.28 Hz, 1 H) 7.74 (t, *J*=7.53 Hz, 1 H) 7.53 - 7.62 (m, 2 H) 5.87 (br. s., 1 H) 5.75 (q, *J*=8.53 Hz, 1 H) 5.01 - 5.08 (m, 1 H) 4.70 (t, *J*=8.53 Hz, 1 H) 4.51 (d, *J*=11.54 Hz, 1 H) 4.18 (d, *J*=6.78 Hz, 1 H) 4.10 (d, *J*=8.28 Hz, 1 H) 4.03 (s, 3 H) 2.62 - 2.78 (m, 2 H) 2.49 (dq, *J*=17.38, 8.93 Hz, 2 H) 1.89 - 2.06 (m, 2 H) 1.72 (dd, *J*=8.03, 5.52 Hz, 1 H) 1.54 - 1.67 (m, 3 H) 1.52 (s, 3 H) 1.37 - 1.49 (m, 3 H) 1.16 - 1.34 (m, 10 H) 1.11 (d, *J*=6.53 Hz, 4 H) 0.86 - 0.96 (m, 5 H); MS: MS *m/z* 766.2 (M^+-1).

Preparation of Compound 4059

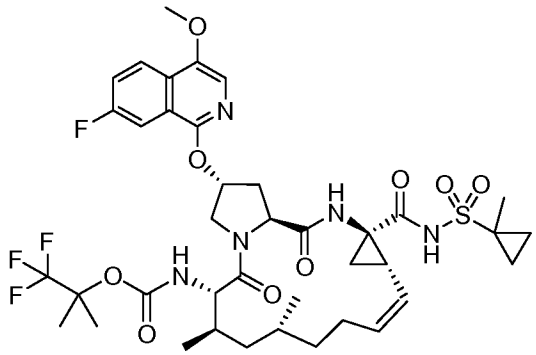


Compound 4059

Compound 4059 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4059: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.19 (dd, *J*=9.03, 5.52 Hz, 1 H) 7.74 - 7.79 (m, 1 H) 7.58 (s, 1 H) 7.51 - 7.56 (m, 1 H) 7.30 (d, *J*=7.78 Hz, 1 H) 5.84 (br. s., 1 H) 5.63 (td, *J*=10.10, 5.90 Hz, 1 H) 5.02 - 5.09 (m, 1 H) 4.74 (d, *J*=11.54 Hz, 1 H) 4.65 (dd, *J*=10.16, 6.90 Hz, 1 H) 3.97 - 4.05 (m, 4 H) 3.77 - 3.85 (m, 1 H) 2.89 - 2.98 (m, 1 H) 2.67 - 2.78 (m, 2 H) 2.43 (ddd, *J*=13.87, 10.10, 4.14 Hz, 2 H) 1.97 (t, *J*=12.67 Hz, 1 H) 1.81 - 1.92 (m, 2 H) 1.79 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.60 (dd, *J*=9.41, 5.65 Hz, 1 H) 1.42 - 1.55 (m, 2 H) 1.36 (s, 2 H) 1.28 - 1.34 (m, 2 H) 1.24 (d, *J*=13.30 Hz, 1 H) 1.07 - 1.20 (m, 2 H) 0.98 - 1.07 (m, 9 H) 0.84 (t, *J*=12.05 Hz, 1 H); MS: MS *m/z* 824.2 (M^+-1).

Preparation of Compound 4060

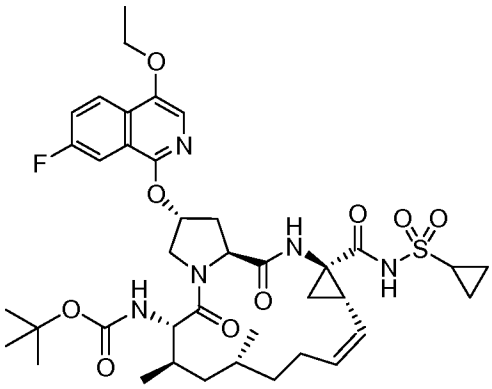


Compound 4060

Compound 4060 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4060: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.19 (dd, *J*=9.29, 5.27 Hz, 1 H) 7.77 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.58 (s, 1 H) 7.52 - 7.56 (m, 1 H) 5.85 (br. s., 1 H) 5.62 (d, *J*=5.02 Hz, 1 H) 5.04 (br. s., 1 H) 4.74 (d, *J*=12.55 Hz, 1 H) 4.66 (dd, *J*=10.04, 6.78 Hz, 1 H) 3.98 - 4.05 (m, 4 H) 3.82 (d, *J*=10.79 Hz, 1 H) 2.70 - 2.79 (m, 2 H) 2.39 - 2.48 (m, 2 H) 1.97 (d, *J*=4.52 Hz, 1 H) 1.88 (d, *J*=6.27 Hz, 1 H) 1.73 - 1.86 (m, 2 H) 1.65 (br. s., 1 H) 1.58 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.53 (s, 3 H) 1.39 - 1.51 (m, 2 H) 1.37 (s, 3 H) 1.18 - 1.32 (m, 2 H) 1.06 (s, 3 H) 0.98 - 1.04 (m, 6 H) 0.77 - 0.95 (m, 3 H); MS: MS *m/z* 838.2 (M^+-1).

Preparation of Compound 4061

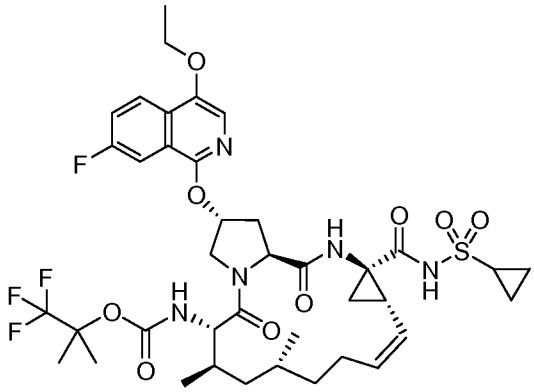


Compound 4061

Compound 4061 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4061: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(4-ethoxy-7-fluoroisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.20 (dd, *J*=9.16, 5.40 Hz, 1 H) 7.93 (s, 1 H) 7.74 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.48 - 7.59 (m, 2 H) 5.84 (br. s., 1 H) 5.63 (d, *J*=4.77 Hz, 1 H) 4.99 - 5.12 (m, 1 H) 4.73 (d, *J*=11.54 Hz, 1 H) 4.59 - 4.66 (m, 1 H) 4.24 (q, *J*=6.94 Hz, 2 H) 3.96 - 4.06 (m, 1 H) 3.85 (d, *J*=10.29 Hz, 1 H) 2.94 (br. s., 1 H) 2.72 (d, *J*=7.78 Hz, 2 H) 2.44 (d, *J*=9.54 Hz, 2 H) 1.98 (br. s., 1 H) 1.74 - 1.89 (m, 2 H) 1.60 (dd, *J*=9.29, 5.02 Hz, 1 H) 1.41 - 1.56 (m, 5 H) 1.29 - 1.38 (m, 1 H) 1.26 (br. s., 1 H) 1.05 - 1.16 (m, 12 H) 0.97 - 1.04 (m, 6 H) 0.77 - 0.88 (m, 1 H); MS: MS *m/z* 786.4 (M^++1).

Preparation of Compound 4062

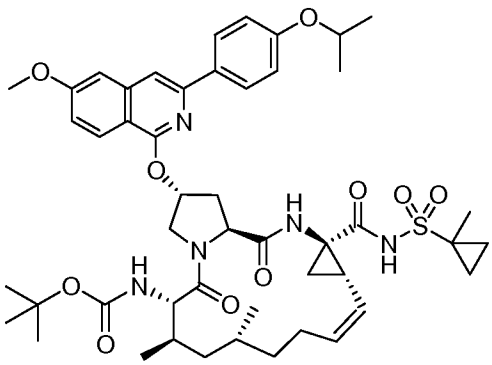


Compound 4062

Compound 4062 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4062: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(4-ethoxy-7-fluoroisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.21 (dd, *J*=9.29, 5.27 Hz, 1 H) 7.93 (s, 1 H) 7.76 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.52 - 7.59 (m, 2 H) 5.81 - 5.86 (m, 1 H) 5.63 (td, *J*=10.10, 5.65 Hz, 1 H) 5.00 - 5.10 (m, 1 H) 4.74 (d, *J*=11.80 Hz, 1 H) 4.61 - 4.67 (m, 1 H) 4.21 - 4.28 (m, 2 H) 3.99 (dd, *J*=11.42, 3.39 Hz, 1 H) 3.81 (d, *J*=10.79 Hz, 1 H) 2.91 - 2.98 (m, 1 H) 2.69 - 2.79 (m, 2 H) 2.43 (ddd, *J*=13.87, 10.10, 4.14 Hz, 2 H) 1.97 (d, *J*=4.27 Hz, 1 H) 1.83 - 1.92 (m, 2 H) 1.76 - 1.82 (m, 2 H) 1.60 (dd, *J*=9.41, 5.40 Hz, 1 H) 1.54 (t, *J*=6.90 Hz, 3 H) 1.44 - 1.51 (m, 2 H) 1.36 (s, 3 H) 1.17 - 1.33 (m, 2 H) 1.07 - 1.17 (m, 2 H) 0.98 - 1.06 (m, 9 H) 0.84 (t, *J*=11.80 Hz, 1 H); MS: MS *m/z* 840.2 (M^++1).

Preparation of Compound 4063

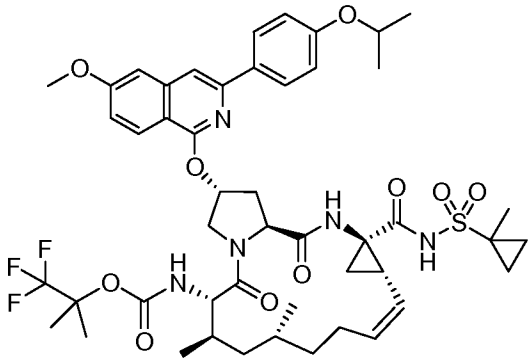


Compound 4063

Compound 4063 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4063: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.02 - 8.14 (m, 3 H) 7.62 - 7.72 (m, 1 H) 7.23 (br. s., 1 H) 6.99 - 7.08 (m, 3 H) 6.09 (br. s., 1 H) 5.45 - 5.81 (m, 1 H) 4.96 - 5.08 (m, 1 H) 4.59 - 4.78 (m, 3 H) 4.08 - 4.23 (m, 1 H) 3.90 - 3.99 (m, 4 H) 2.66 - 2.86 (m, 2 H) 2.39 - 2.59 (m, 2 H) 1.93 - 2.05 (m, 1 H) 1.55 - 1.90 (m, 5 H) 1.52 (d, *J*=5.77 Hz, 4 H) 1.40 - 1.48 (m, 2 H) 1.34 - 1.39 (m, 7 H) 1.26 - 1.32 (m, 4 H) 1.18 - 1.24 (m, 5 H) 1.12 (d, *J*=6.02 Hz, 2 H) 0.97 - 1.06 (m, 4 H) 0.81 - 0.96 (m, 3 H); MS: MS *m/z* 902.8 (M^++1).

Preparation of Compound 4064

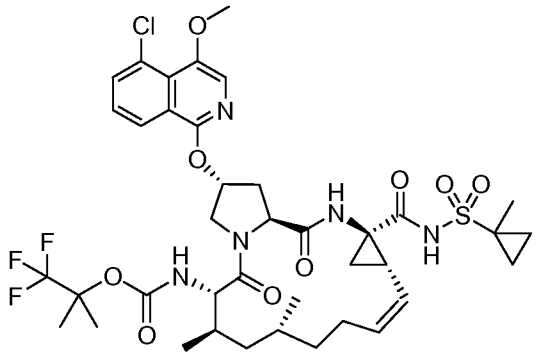


Compound 4064

Compound 4064 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4064: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.05 - 8.16 (m, 3 H) 7.70 (s, 1 H) 7.25 (d, *J*=2.51 Hz, 1 H) 6.99 - 7.10 (m, 3 H) 6.08 (br. s., 1 H) 5.64 (td, *J*=10.35, 5.40 Hz, 1 H) 5.02 (t, *J*=9.91 Hz, 1 H) 4.80 (d, *J*=12.05 Hz, 1 H) 4.60 - 4.75 (m, 2 H) 4.14 (dd, *J*=11.42, 3.64 Hz, 1 H) 3.96 (s, 3 H) 3.84 - 3.92 (m, 1 H) 2.71 - 2.86 (m, 2 H) 2.39 - 2.59 (m, 2 H) 1.78 (dd, *J*=8.41, 5.65 Hz, 3 H) 1.67 (d, *J*=11.04 Hz, 1 H) 1.57 - 1.61 (m, 1 H) 1.53 (s, 3 H) 1.43 - 1.50 (m, 2 H) 1.34 - 1.41 (m, 10 H) 1.31 (s, 2 H) 1.11 (s, 3 H) 1.01 (dd, *J*=14.56, 6.78 Hz, 6 H) 0.80 - 0.94 (m, 3 H); MS: MS *m/z* 956.9 (M^++1).

Preparation of Compound 4065

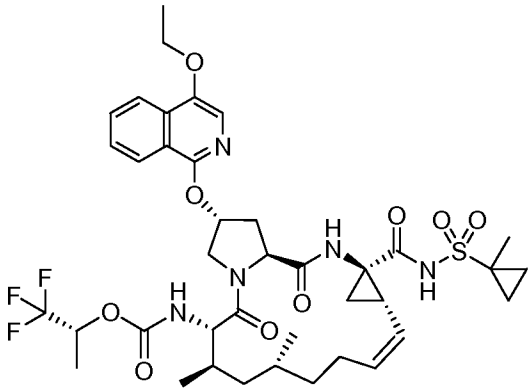


Compound 4065

Compound 4065 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4065: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(5-chloro-4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.18 (dd, *J*=8.41, 1.13 Hz, 1 H) 7.78 (dd, *J*=7.65, 1.13 Hz, 1 H) 7.72 (s, 1 H) 7.48 (t, *J*=7.91 Hz, 1 H) 5.83 - 5.86 (m, 1 H) 5.57 - 5.68 (m, 1 H) 5.01 (t, *J*=10.16 Hz, 1 H) 4.78 (d, *J*=12.05 Hz, 1 H) 4.67 (dd, *J*=10.29, 7.03 Hz, 1 H) 4.01 (dd, *J*=11.67, 3.39 Hz, 1 H) 3.98 (s, 3 H) 3.74 - 3.84 (m, 1 H) 3.38 (dt, *J*=3.26, 1.63 Hz, 1 H) 3.28 (dt, *J*=3.33, 1.73 Hz, 1 H) 2.68 - 2.80 (m, 2 H) 2.45 (ddd, *J*=13.68, 10.16, 4.02 Hz, 2 H) 1.81 - 2.03 (m, 3 H) 1.78 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.64 - 1.71 (m, 1 H) 1.58 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.53 (s, 2 H) 1.41 - 1.51 (m, 2 H) 1.36 (s, 3 H) 1.21 - 1.32 (m, 1 H) 1.00 (dd, *J*=12.30, 6.78 Hz, 6 H) 0.96 (s, 3 H) 0.79 - 0.93 (m, 3 H); MS: MS *m/z* 857.1 (M^++1).

Preparation of Compound 4066

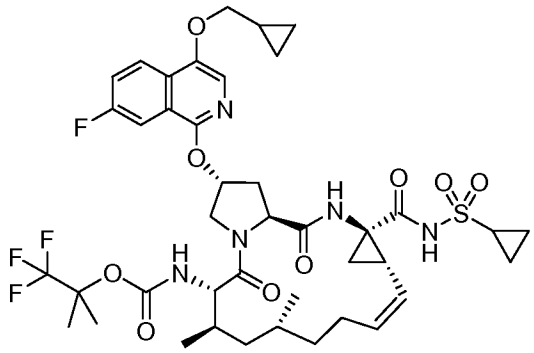


Compound 4066

Compound 4066 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4066: (R)-1,1,1-trifluoropropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.14 (d, *J*=9.04 Hz, 2 H) 7.70 - 7.76 (m, 1 H) 7.55 (s, 1 H) 7.50 - 7.54 (m, 1 H) 5.86 (br. s., 1 H) 5.58 - 5.67 (m, 1 H) 5.02 (t, *J*=9.79 Hz, 1 H) 4.74 (d, *J*=11.04 Hz, 1 H) 4.64 (dd, *J*=10.16, 7.15 Hz, 1 H) 4.50 (quin, *J*=6.78 Hz, 1 H) 4.25 (q, *J*=7.03 Hz, 2 H) 4.03 (dd, *J*=11.29, 3.26 Hz, 1 H) 3.89 (d, *J*=10.79 Hz, 1 H) 2.69 - 2.79 (m, 2 H) 2.43 (ddd, *J*=13.68, 9.91, 4.02 Hz, 2 H) 1.92 (d, *J*=7.53 Hz, 2 H) 1.72 - 1.85 (m, 2 H) 1.66 (d, *J*=11.04 Hz, 1 H) 1.49 - 1.60 (m, 9 H) 1.40 - 1.49 (m, 1 H) 1.22 - 1.32 (m, 1 H) 1.20 (d, *J*=6.78 Hz, 3 H) 0.97 - 1.05 (m, 6 H) 0.82 - 0.95 (m, 3 H); MS: MS *m/z* 820.4 (M^+-1).

Preparation of Compound 4067

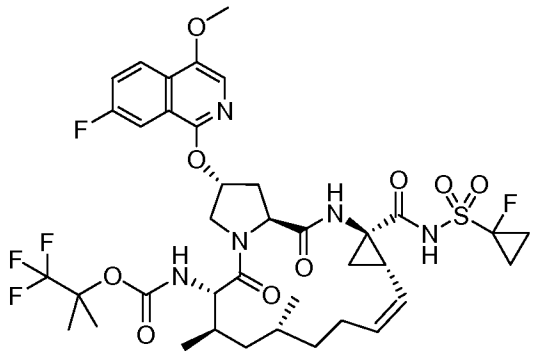


Compound 4067

Compound 4067 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4067: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-(cyclopropylmethoxy)-7-fluoroisoquinolin-1-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.24 (dd, *J*=9.16, 5.40 Hz, 1 H) 7.76 (dd, *J*=9.41, 2.38 Hz, 1 H) 7.48 - 7.61 (m, 2 H) 5.82 (br. s., 1 H) 5.61 (br. s., 1 H) 4.73 (d, *J*=12.30 Hz, 1 H) 4.61 - 4.67 (m, 1 H) 3.94 - 4.06 (m, 3 H) 3.81 (d, *J*=11.04 Hz, 1 H) 2.90 (br. s., 1 H) 2.65 - 2.80 (m, 2 H) 2.44 (br. s., 2 H) 1.70 - 2.03 (m, 4 H) 1.45 - 1.66 (m, 3 H) 1.21 - 1.44 (m, 9 H) 0.97 - 1.11 (m, 9 H) 0.78 - 0.94 (m, 2 H) 0.64 - 0.74 (m, 2 H) 0.39 - 0.49 (m, 2 H); MS: MS *m/z* 866.2 (M^++1).

Preparation of Compound 4068

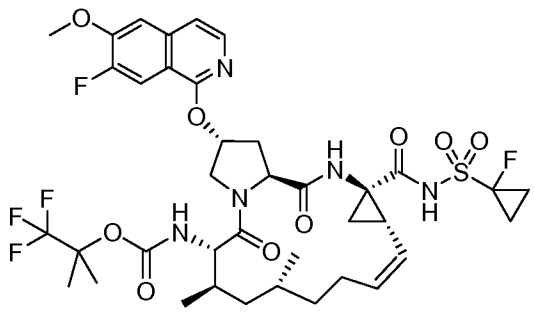


Compound 4068

Compound 4068 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4068: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17 (dd, *J*=9.13, 5.38 Hz, 1 H) 7.90 (s, 1 H) 7.74 (dd, *J*=9.51, 2.50 Hz, 1 H) 7.50 - 7.57 (m, 2 H) 5.83 (s, 1 H) 5.53 - 5.64 (m, 1 H) 4.98 (t, *J*=10.01 Hz, 1 H) 4.73 (s, 1 H) 4.64 (dd, *J*=10.38, 6.88 Hz, 1 H) 3.97 - 4.02 (m, 4 H) 3.79 (d, *J*=10.76 Hz, 1 H) 2.68 - 2.77 (m, 2 H) 2.34 - 2.46 (m, 2 H) 1.80 - 2.00 (m, 2 H) 1.70 - 1.79 (m, 2 H) 1.56 - 1.68 (m, 3 H) 1.41 - 1.53 (m, 3 H) 1.34 (s, 2 H) 1.29 (s, 2 H) 1.18 - 1.25 (m, 1 H) 0.95 - 1.05 (m, 6 H) 0.77 - 0.92 (m, 3 H); MS: MS *m/z* 844.2 (M^++1).

Preparation of Compound 4069

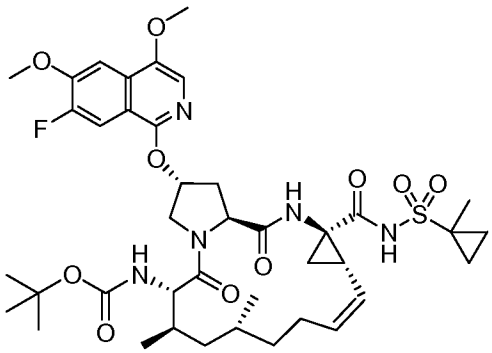


Compound 4069

Compound 4069 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4069: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.04 (s, 1 H) 7.95 (d, *J*=5.77 Hz, 1 H) 7.79 (d, *J*=11.80 Hz, 1 H) 7.41 (d, *J*=8.28 Hz, 1 H) 7.31 (d, *J*=6.02 Hz, 1 H) 5.90 (s, 1 H) 5.62 (d, *J*=6.02 Hz, 1 H) 5.01 (t, *J*=9.79 Hz, 1 H) 4.73 (d, *J*=11.29 Hz, 1 H) 4.66 (dd, *J*=10.16, 6.90 Hz, 1 H) 3.99 - 4.06 (m, 4 H) 3.83 (dd, *J*=10.92, 8.16 Hz, 1 H) 2.71 - 2.79 (m, 2 H) 2.37 - 2.50 (m, 2 H) 1.72 - 1.83 (m, 2 H) 1.56 - 1.70 (m, 3 H) 1.44 - 1.55 (m, 3 H) 1.39 (s, 2 H) 1.30 - 1.35 (m, 3 H) 1.13 (s, 3 H) 1.01 (t, *J*=7.15 Hz, 6 H) 0.82 - 0.93 (m, 2 H); MS: MS *m/z* 844.6 (M^++1).

Preparation of Compound 4070

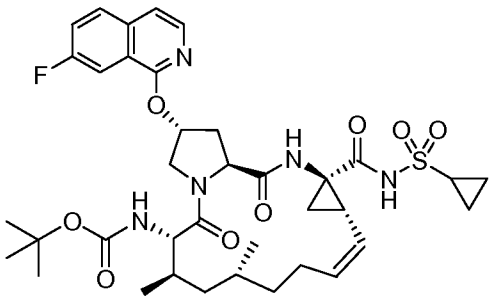


Compound 4070

Compound 4070 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4070: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.22 (s, 1 H) 6.92 (d, *J*=11.54 Hz, 1 H) 6.70 - 6.79 (m, 2 H) 5.02 (br. s., 1 H) 4.82 (d, *J*=5.52 Hz, 1 H) 4.20 (t, *J*=10.04 Hz, 1 H) 3.75 - 3.91 (m, 2 H) 3.22 (d, *J*=1.51 Hz, 7 H) 3.02 - 3.07 (m, 1 H) 1.89 - 1.97 (m, 2 H) 1.56 - 1.68 (m, 2 H) 1.17 (br. s., 1 H) 0.89 - 1.09 (m, 3 H) 0.74 - 0.87 (m, 2 H) 0.72 (s, 3 H) 0.58 - 0.67 (m, 2 H) 0.35 (s, 9 H) 0.20 (dd, *J*=9.03, 6.78 Hz, 6 H) -0.01 - 0.13 (m, 4 H); MS: MS *m/z* 816.2 (M^++1).

Preparation of Compound 4071

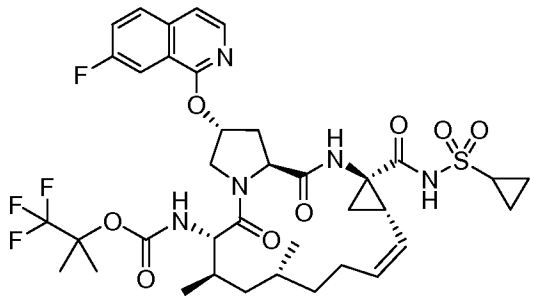


Compound 4071

Compound 4071 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4071: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-fluoroisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.00 (d, *J*=5.77 Hz, 1 H) 7.88 - 7.93 (m, 1 H) 7.81 (dd, *J*=9.54, 2.76 Hz, 1 H) 7.56 (d, *J*=2.76 Hz, 1 H) 7.36 - 7.39 (m, 1 H) 5.94 (br. s., 1 H) 5.62 (d, *J*=5.77 Hz, 1 H) 4.76 (d, *J*=11.04 Hz, 1 H) 4.61 - 4.67 (m, 1 H) 4.04 (dd, *J*=11.67, 3.39 Hz, 1 H) 3.85 (d, *J*=10.79 Hz, 1 H) 2.94 (br. s., 1 H) 2.72 - 2.79 (m, 2 H) 2.40 - 2.50 (m, 2 H) 1.97 - 2.03 (m, 1 H) 1.76 - 1.89 (m, 3 H) 1.60 (dd, *J*=9.41, 5.40 Hz, 1 H) 1.43 - 1.54 (m, 3 H) 1.20 - 1.38 (m, 4 H) 1.08 - 1.13 (m, 9 H) 1.01 (dd, *J*=13.30, 6.78 Hz, 6 H) 0.89 - 0.96 (m, 1 H) 0.81 (s, 1 H); MS: MS *m/z* 742.4 (M^++1).

Preparation of Compound 4072

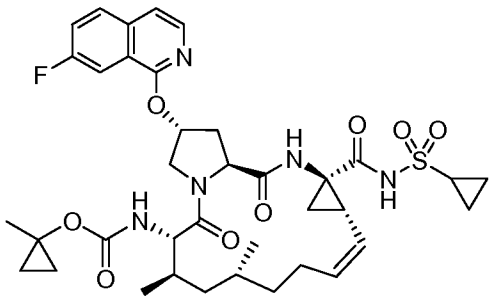


Compound 4072

Compound 4072 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4072: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-fluoroisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.01 (d, *J*=5.77 Hz, 1 H) 7.92 (dd, *J*=9.03, 5.27 Hz, 1 H) 7.83 (dd, *J*=9.29, 2.76 Hz, 1 H) 7.56 (td, *J*=8.85, 2.64 Hz, 1 H) 7.39 (d, *J*=5.52 Hz, 1 H) 5.92 (br. s., 1 H) 5.62 (d, *J*=5.52 Hz, 1 H) 5.09 (br. s., 1 H) 4.77 (d, *J*=10.29 Hz, 1 H) 4.61 - 4.70 (m, 1 H) 4.02 (dd, *J*=11.67, 3.39 Hz, 1 H) 3.81 (d, *J*=10.79 Hz, 1 H) 2.94 (br. s., 1 H) 2.68 - 2.81 (m, 2 H) 2.37 - 2.50 (m, 2 H) 1.74 - 2.00 (m, 4 H) 1.60 (dd, *J*=9.54, 5.27 Hz, 1 H) 1.44 - 1.53 (m, 2 H) 1.30 - 1.36 (m, 5 H) 1.10 (dt, *J*=9.72, 4.80 Hz, 2 H) 0.99 - 1.06 (m, 10 H) 0.80 - 0.89 (m, 1 H); MS: MS *m/z* 796.2 (M^++1).

Preparation of Compound 4073

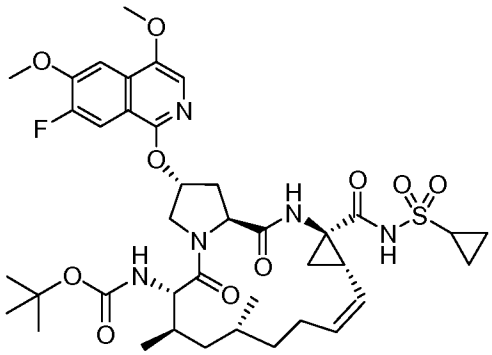


Compound 4073

Compound 4073 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4073: 1-methylcyclopropyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-fluoroisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.01 (d, *J*=5.77 Hz, 1 H) 7.92 (dd, *J*=9.03, 5.27 Hz, 1 H) 7.84 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.55 (td, *J*=8.85, 2.64 Hz, 1 H) 7.39 (d, *J*=5.77 Hz, 1 H) 5.97 (br. s., 1 H) 5.61 (br. s., 1 H) 5.07 (br. s., 1 H) 4.69 (d, *J*=12.30 Hz, 1 H) 4.57 - 4.64 (m, 1 H) 4.09 (dd, *J*=11.42, 3.64 Hz, 1 H) 3.92 (d, *J*=10.79 Hz, 1 H) 2.94 (br. s., 1 H) 2.76 (dd, *J*=14.18, 7.40 Hz, 2 H) 2.40 - 2.51 (m, 2 H) 1.74 - 2.03 (m, 5 H) 1.59 (dd, *J*=9.41, 5.14 Hz, 1 H) 1.49 (br. s., 2 H) 1.31 (br. s., 2 H) 1.20 (s, 3 H) 1.09 (dd, *J*=9.91, 4.89 Hz, 2 H) 1.02 (dd, *J*=14.93, 6.65 Hz, 7 H) 0.86 (t, *J*=11.92 Hz, 1 H) 0.63 - 0.70 (m, 1 H) 0.54 (dt, *J*=11.23, 5.55 Hz, 1 H) 0.40 - 0.47 (m, 1 H) 0.31 - 0.39 (m, 1 H); MS: MS *m/z* 738.2 (M^++1).

Preparation of Compound 4074

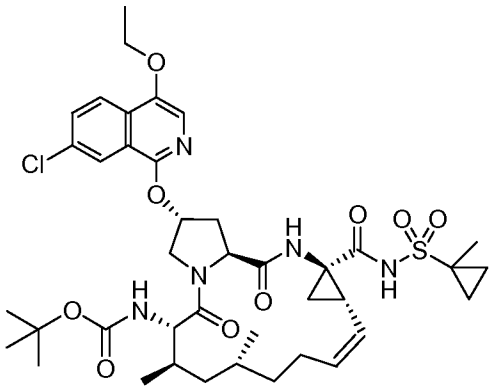


Compound 4074

Compound 4074 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4074: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.73 (d, *J*=11.54 Hz, 1 H) 7.49 - 7.58 (m, 2 H) 6.63 (d, *J*=7.53 Hz, 1 H) 5.81 (br. s., 1 H) 5.62 (d, *J*=4.77 Hz, 1 H) 5.06 (br. s., 1 H) 4.56 - 4.70 (m, 2 H) 3.98 - 4.05 (m, 7 H) 3.81 - 3.90 (m, 1 H) 3.07 (q, *J*=7.28 Hz, 1 H) 2.92 (br. s., 1 H) 2.65 - 2.78 (m, 2 H) 2.42 (br. s., 2 H) 1.98 (br. s., 1 H) 1.73 - 1.88 (m, 2 H) 1.59 (dd, *J*=9.29, 5.27 Hz, 1 H) 1.49 (br. s., 1 H) 1.28 - 1.36 (m, 3 H) 1.20 - 1.27 (m, 1 H) 1.16 (s, 9 H) 1.11 (br. s., 1 H) 1.01 (dd, *J*=13.05, 6.78 Hz, 6 H) 0.73 - 0.89 (m, 1 H); MS: MS *m/z* 802.8 (M^++1).

Preparation of Compound 4075

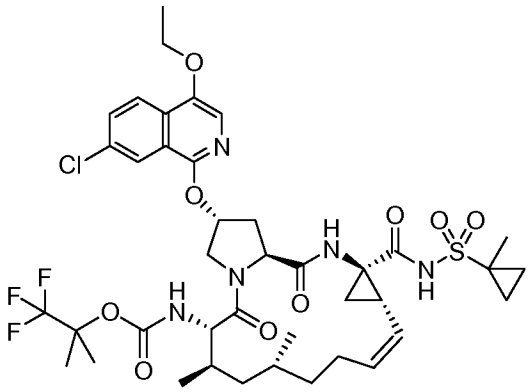


Compound 4075

Compound 4075 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4075: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-chloro-4-ethoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.13 (d, *J*=9.03 Hz, 1 H) 8.07 (d, *J*=2.01 Hz, 1 H) 7.70 (dd, *J*=8.91, 2.13 Hz, 1 H) 7.60 (s, 1 H) 6.66 (d, *J*=8.53 Hz, 1 H) 5.87 (br. s., 1 H) 5.63 (td, *J*=10.23, 5.65 Hz, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.60 - 4.76 (m, 2 H) 4.24 (q, *J*=6.86 Hz, 2 H) 4.03 (dd, *J*=11.54, 3.26 Hz, 1 H) 3.79 - 3.86 (m, 1 H) 2.69 - 2.80 (m, 2 H) 2.44 (ddd, *J*=13.74, 9.98, 4.39 Hz, 2 H) 1.98 (br. s., 1 H) 1.75 - 1.89 (m, 3 H) 1.64 - 1.71 (m, 1 H) 1.55 - 1.62 (m, 2 H) 1.51 - 1.54 (m, 6 H) 1.40 - 1.49 (m, 3 H) 1.13 - 1.33 (m, 3 H) 1.05 (s, 9 H) 0.96 - 1.02 (m, 6 H) 0.80 - 0.91 (m, 2 H); MS: MS *m/z* 816.2 (M^++1).

Preparation of Compound 4076

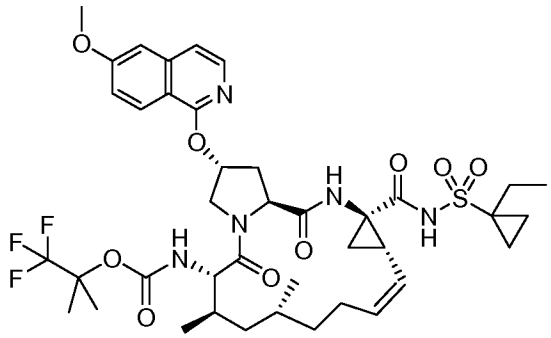


Compound 4076

Compound 4076 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4076: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-chloro-4-ethoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.15 (d, *J*=9.03 Hz, 1 H) 8.08 (d, *J*=2.01 Hz, 1 H) 7.72 (dd, *J*=8.91, 2.13 Hz, 1 H) 7.61 (s, 1 H) 5.86 (br. s., 1 H) 5.62 (d, *J*=5.52 Hz, 1 H) 5.01 (d, *J*=12.05 Hz, 1 H) 4.66 - 4.78 (m, 2 H) 4.25 (q, *J*=7.03 Hz, 2 H) 4.00 (dd, *J*=11.54, 3.26 Hz, 1 H) 3.77 (d, *J*=10.79 Hz, 1 H) 2.74 (dd, *J*=13.05, 6.78 Hz, 2 H) 2.38 - 2.51 (m, 2 H) 1.91 - 2.02 (m, 1 H) 1.75 - 1.90 (m, 3 H) 1.57 - 1.72 (m, 2 H) 1.51 - 1.57 (m, 7 H) 1.39 - 1.49 (m, 3 H) 1.31 (s, 1 H) 1.21 - 1.28 (m, 3 H) 1.00 (dd, *J*=12.92, 6.65 Hz, 6 H) 0.94 (s, 3 H) 0.78 - 0.90 (m, 2 H); MS: MS *m/z* 870.2 (M^++1).

Preparation of Compound 4077

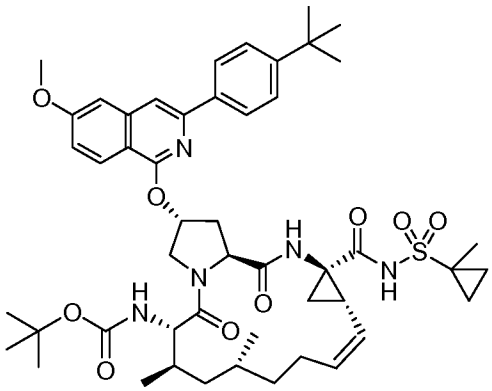


Compound 4077

Compound 4077 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4077: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-ethylcyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.06 (s, 1 H) 8.12 (d, *J*=9.04 Hz, 1 H) 7.82 - 8.00 (m, 1 H) 7.30 (d, *J*=6.27 Hz, 1 H) 7.23 (d, *J*=2.26 Hz, 1 H) 7.13 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.89 (br. s., 1 H) 5.50 - 5.71 (m, 1 H) 4.99 (t, *J*=9.91 Hz, 1 H) 4.76 (d, *J*=11.04 Hz, 1 H) 4 4.05 (dd, *J*=11.54, 3.51 Hz, 1 H) 3.95 (s, 3 H) 3.84 (d, *J*=10.79 Hz, 1 H) 2.66 - 2.80 (m, 2 H) 2.34 - 2.52 (m, 2 H) 2.01 - 2.12 (m, 1 H) 1.86 - 2.00 (m, 2 H) 1.73 - 1.85 (m, 3 H) 1.60 - 1.71 (m, 1 H) 1.56 (dd, *J*=9.41, 5.65 Hz, 1 H) 1.43 - 1.52 (m, 2 H) 1.35 - 1.43 (m, 4 H) 1.19 - 1.34 (m, 2 H) 0.96 - 1.06 (m, 12 H) 0.76 - 0.95 (m, 3 H); MS: MS *m/z* 836.4 (M^++1).

Preparation of Compound 4078

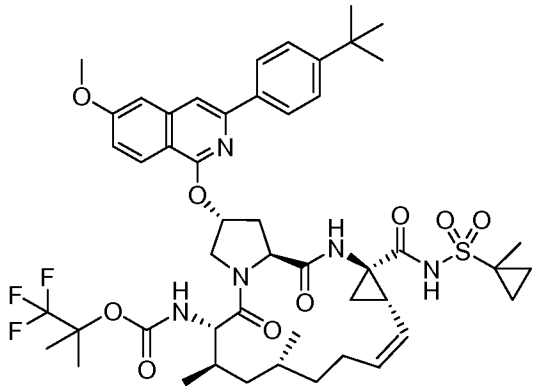


Compound 4078

Compound 4078 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4078: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(3-(4-tert-butylphenyl)-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.06 - 8.13 (m, 3 H) 7.76 (s, 1 H) 7.55 (d, *J*=8.53 Hz, 2 H) 7.27 (d, *J*=2.26 Hz, 1 H) 7.06 (d, *J*=9.29 Hz, 1 H) 6.11 (br. s., 1 H) 5.58 - 5.67 (m, 1 H) 5.04 (br. s., 1 H) 4.59 - 4.74 (m, 2 H) 4.19 (d, *J*=8.28 Hz, 1 H) 3.90 - 3.99 (m, 4 H) 2.71 - 2.87 (m, 3 H) 2.42 - 2.57 (m, 2 H) 1.97 (s, 1 H) 1.74 - 1.92 (m, 3 H) 1.66 (d, *J*=8.78 Hz, 1 H) 1.44 - 1.60 (m, 6 H) 1.41 (s, 9 H) 1.27 - 1.37 (m, 2 H) 1.22 (s, 9 H) 1.02 (dd, *J*=13.43, 6.65 Hz, 6 H) 0.84 - 0.94 (m, 2 H);MS: MS *m/z* 900.9 (M^++1).

Preparation of Compound 4079

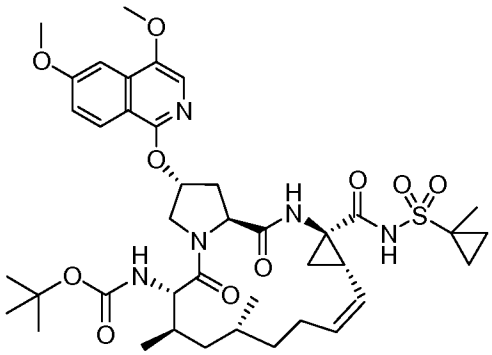


Compound 4079

Compound 4079 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4079: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(3-(4-tert-butylphenyl)-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.07 - 8.13 (m, 3 H) 7.77 (s, 1 H) 7.55 (d, *J*=8.53 Hz, 2 H) 7.25 - 7.31 (m, 1 H) 7.07 (dd, *J*=9.03, 2.26 Hz, 1 H) 6.09 (br. s., 1 H) 5.64 (td, *J*=10.10, 5.90 Hz, 1 H) 5.02 (t, *J*=9.91 Hz, 1 H) 4.78 (s, 1 H) 4.69 (dd, *J*=9.91, 7.15 Hz, 1 H) 4.16 (dd, *J*=11.29, 3.51 Hz, 1 H) 3.97 (s, 3 H) 3.90 (dd, *J*=10.67, 8.41 Hz, 1 H) 2.71 - 2.86 (m, 2 H) 2.41 - 2.56 (m, 2 H) 1.95 - 2.06 (m, 1 H) 1.74 - 1.93 (m, 3 H) 1.64 - 1.70 (m, 1 H) 1.58 (dd, *J*=9.66, 5.65 Hz, 1 H) 1.54 (s, 3 H) 1.43 - 1.51 (m, 3 H) 1.41 (s, 11 H) 1.21 - 1.36 (m, 2 H) 1.11 (s, 3 H) 1.01 (dd, *J*=15.69, 6.65 Hz, 6 H) 0.85 - 0.92 (m, 3 H);MS: MS *m/z* 952.9 (M^+-1).

Preparation of Compound 4080

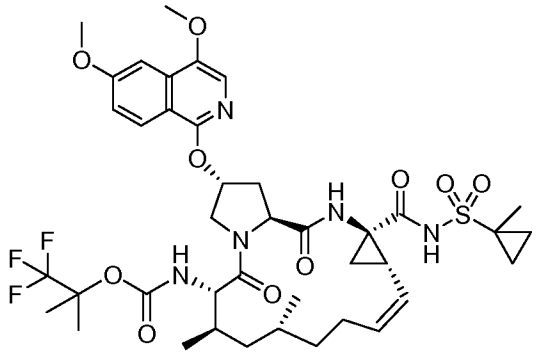


Compound 4080

Compound 4080 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4080: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4,6-dimethoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.04 (d, *J*=9.03 Hz, 1 H) 7.49 (s, 1 H) 7.39 (d, *J*=2.26 Hz, 1 H) 7.09 (dd, *J*=9.16, 2.38 Hz, 1 H) 5.79 (br. s., 1 H) 5.60 (td, *J*=10.10, 5.90 Hz, 1 H) 4.98 (t, *J*=9.91 Hz, 1 H) 4.52 - 4.68 (m, 2 H) 3.96 - 4.03 (m, 4 H) 3.92 (s, 3 H) 3.85 (d, *J*=10.79 Hz, 1 H) 2.66 - 2.76 (m, 2 H) 2.32 - 2.46 (m, 2 H) 1.95 (t, *J*=13.30 Hz, 1 H) 1.73 (dd, *J*=8.28, 5.77 Hz, 3 H) 1.63 (d, *J*=10.54 Hz, 1 H) 1.38 - 1.56 (m, 6 H) 1.28 (s, 2 H) 1.14 (s, 9 H) 0.98 (dd, *J*=9.91, 6.65 Hz, 6 H) 0.81 - 0.88 (m, 3 H);MS: MS *m/z* 798.5 (M^++1).

Preparation of Compound 4081

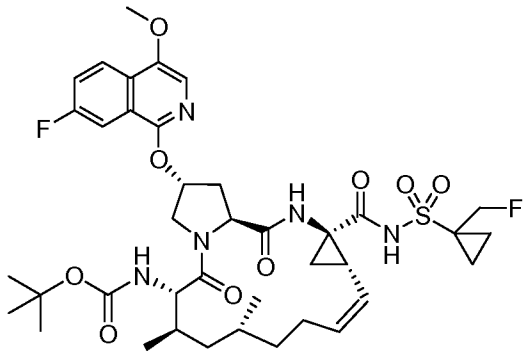


Compound 4081

Compound 4081 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4081: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4,6-dimethoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.04 (d, *J*=9.03 Hz, 1 H) 7.49 (s, 1 H) 7.39 (d, *J*=2.26 Hz, 1 H) 7.09 (dd, *J*=9.16, 2.38 Hz, 1 H) 5.79 (br. s., 1 H) 5.60 (td, *J*=10.10, 5.90 Hz, 1 H) 4.98 (t, *J*=9.91 Hz, 1 H) 4.52 - 4.69 (m, 2 H) 3.97 - 4.03 (m, 4 H) 3.82 - 3.93 (m, 4 H) 2.64 - 2.76 (m, 2 H) 2.33 - 2.46 (m, 2 H) 1.95 (t, *J*=13.30 Hz, 1 H) 1.70 - 1.88 (m, 3 H) 1.60 - 1.68 (m, 1 H) 1.52 - 1.56 (m, 1 H) 1.49 (s, 3 H) 1.36 - 1.45 (m, 2 H) 1.20 - 1.31 (m, 2 H) 1.08 - 1.16 (m, 10 H) 0.98 (dd, *J*=9.91, 6.65 Hz, 6 H) 0.79 - 0.89 (m, 3 H); MS: MS *m/z* 852.6 (M^++1).

Preparation of Compound 4082

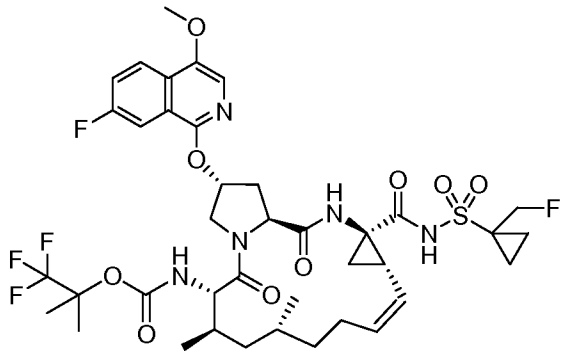


Compound 4082

Compound 4082 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4082: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17 (dd, *J*=9.16, 5.40 Hz, 1 H) 7.74 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.55 - 7.57 (m, 1 H) 7.49 - 7.54 (m, 1 H) 5.84 (br. s., 1 H) 5.62 (td, *J*=10.23, 5.65 Hz, 1 H) 5.00 (t, *J*=10.16 Hz, 1 H) 4.71 (d, *J*=11.80 Hz, 1 H) 4.59 - 4.66 (m, 2 H) 4.50 (s, 1 H) 3.99 - 4.06 (m, 4 H) 3.85 (d, *J*=10.79 Hz, 1 H) 2.68 - 2.76 (m, 2 H) 2.40 - 2.49 (m, 2 H) 1.91 - 2.02 (m, 1 H) 1.77 - 1.89 (m, 2 H) 1.62 - 1.74 (m, 3 H) 1.57 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.43 - 1.53 (m, 2 H) 1.17 - 1.35 (m, 3 H) 1.12 (s, 9 H) 1.01 (dd, *J*=14.05, 6.78 Hz, 6 H) 0.80 - 0.92 (m, 1 H); MS: MS *m/z* 804.4 (M^++1).

Preparation of Compound 4083

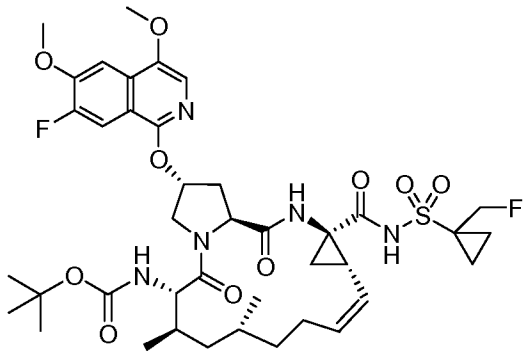


Compound 4083

Compound 4083 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4083: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.19 (dd, *J*=9.03, 5.27 Hz, 1 H) 7.76 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.47 - 7.59 (m, 2 H) 5.83 (br. s., 1 H) 5.59 (br. s., 1 H) 4.68 - 4.76 (m, 1 H) 4.55 - 4.66 (m, 2 H) 3.98 - 4.05 (m, 4 H) 3.82 (d, *J*=11.04 Hz, 1 H) 2.73 (dd, *J*=14.05, 6.78 Hz, 1 H) 2.34 - 2.50 (m, 2 H) 2.06 (s, 2 H) 1.97 (t, *J*=14.05 Hz, 1 H) 1.78 - 1.90 (m, 2 H) 1.61 - 1.75 (m, 2 H) 1.57 (dd, *J*=9.41, 5.40 Hz, 1 H) 1.48 (br. s., 3 H) 1.37 (s, 3 H) 1.31 (s, 2 H) 1.12 - 1.28 (m, 3 H) 0.97 - 1.07 (m, 9 H) 0.79 - 0.95 (m, 1 H); MS: MS *m/z* 859.2 (M^++1).

Preparation of Compound 4084

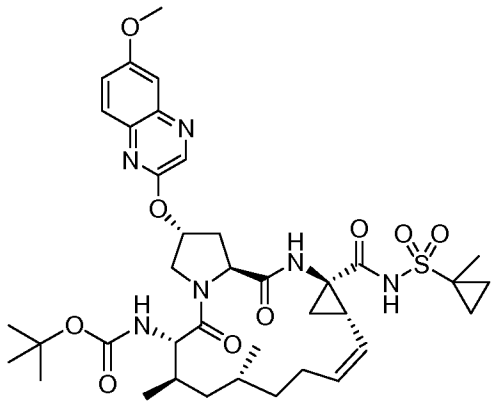


Compound 4084

Compound 4084 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4084: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.73 (d, *J*=11.54 Hz, 1 H) 7.51 - 7.58 (m, 2 H) 5.82 (br. s., 1 H) 5.62 (td, *J*=10.23, 5.90 Hz, 1 H) 4.96 - 5.05 (m, 1 H) 4.79 (d, *J*=11.29 Hz, 1 H) 4.48 - 4.70 (m, 3 H) 3.97 - 4.06 (m, 7 H) 3.81 - 3.90 (m, 1 H) 2.64 - 2.76 (m, 2 H) 2.42 (ddd, *J*=13.99, 10.10, 4.52 Hz, 2 H) 1.97 (t, *J*=12.80 Hz, 1 H) 1.76 - 1.90 (m, 2 H) 1.62 - 1.75 (m, 2 H) 1.55 - 1.61 (m, 1 H) 1.45 - 1.53 (m, 1 H) 1.39 (dt, *J*=6.96, 3.67 Hz, 1 H) 1.30 - 1.35 (m, 1 H) 1.20 - 1.29 (m, 3 H) 1.16 (s, 9 H) 1.01 (dd, *J*=13.05, 6.53 Hz, 6 H) 0.84 (t, *J*=12.30 Hz, 1 H); MS: MS *m/z* 834.4 (M^++1).

Preparation of Compound 4085

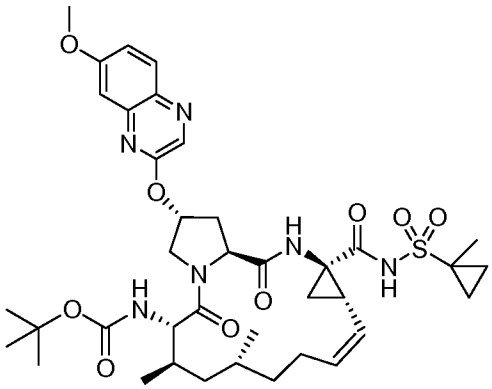


Compound 4085

Compound 4085 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4085: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(6-methoxyquinoxalin-2-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.39 (s, 1 H) 7.83 (d, *J*=9.03 Hz, 1 H) 7.39 (d, *J*=2.51 Hz, 2 H) 6.65 (d, *J*=8.78 Hz, 1 H) 5.89 (br. s., 1 H) 5.63 (td, *J*=10.23, 5.65 Hz, 1 H) 5.02 (t, *J*=9.66 Hz, 1 H) 4.69 (d, *J*=11.80 Hz, 1 H) 4.61 (dd, *J*=10.04, 7.28 Hz, 1 H) 4.08 (dd, *J*=11.92, 3.39 Hz, 1 H) 3.96 (s, 3 H) 3.80 - 3.87 (m, 1 H) 2.66 - 2.76 (m, 2 H) 2.39 - 2.52 (m, 2 H) 1.99 (br. s., 1 H) 1.86 (d, *J*=6.53 Hz, 1 H) 1.78 (dd, *J*=8.28, 5.52 Hz, 2 H) 1.63 - 1.70 (m, 1 H) 1.59 (dd, *J*=9.41, 5.65 Hz, 1 H) 1.53 (s, 3 H) 1.40 - 1.50 (m, 3 H) 1.31 (s, 2 H) 1.21 - 1.28 (m, 1 H) 1.16 (s, 9 H) 0.95 - 1.04 (m, 6 H) 0.77 - 0.91 (m, 1 H); MS: MS *m/z* 768.1 (M^+-1).

Preparation of Compound 4086

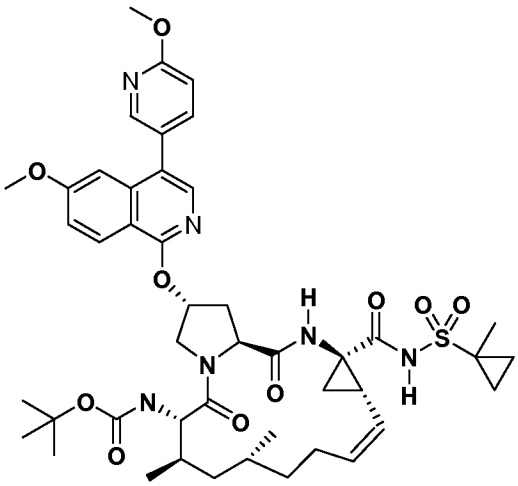


Compound 4086

Compound 4086 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4086: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-methoxyquinoxalin-2-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.26 (s, 1 H) 7.86 (d, *J*=9.03 Hz, 1 H) 7.33 (d, *J*=2.76 Hz, 1 H) 7.27 (dd, *J*=9.03, 2.76 Hz, 1 H) 6.70 (d, *J*=8.78 Hz, 1 H) 5.92 (br. s., 1 H) 5.64 (s, 1 H) 4.97 - 5.06 (m, 1 H) 4.72 (d, *J*=11.04 Hz, 1 H) 4.59 - 4.65 (m, 1 H) 4.10 (d, *J*=11.54 Hz, 1 H) 3.99 (s, 3 H) 3.81 - 3.87 (m, 1 H) 2.70 (d, *J*=7.03 Hz, 2 H) 2.49 (s, 2 H) 1.99 (br. s., 1 H) 1.87 (br. s., 1 H) 1.74 - 1.82 (m, 2 H) 1.67 (d, *J*=12.05 Hz, 1 H) 1.59 (dd, *J*=9.66, 5.65 Hz, 1 H) 1.53 (s, 3 H) 1.48 (br. s., 1 H) 1.38 - 1.46 (m, 2 H) 1.31 (s, 2 H) 1.22 (br. s., 1 H) 1.15 (s, 9 H) 0.99 (dd, *J*=19.83, 6.53 Hz, 6 H) 0.90 (br. s., 1 H); MS: MS *m/z* 769.4 (M^++1).

Preparation of Compound 4087

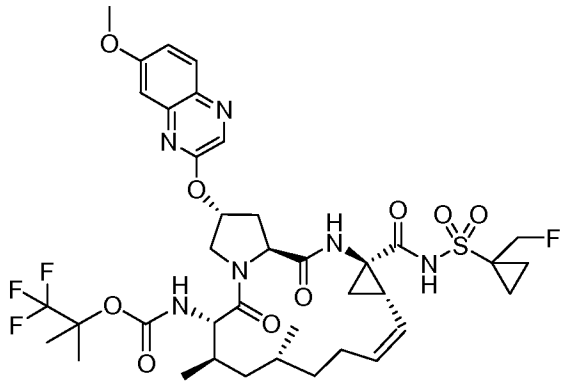


Compound 4087

Compound 4087 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4087: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(6-methoxy-4-(6-methoxypyridin-3-yl)isoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.07 (s, 1 H) 8.22 - 8.26 (m, 2 H) 7.84 - 7.90 (m, 2 H) 7.18 (dd, *J*=9.16, 2.38 Hz, 1 H) 7.01 - 7.06 (m, 2 H) 5.94 (br. s., 1 H) 5.63 (d, *J*=5.27 Hz, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.78 - 4.84 (m, 1 H) 4.67 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.03 (s, 4 H) 3.81 - 3.90 (m, 4 H) 2.71 - 2.83 (m, 2 H) 2.47 (ddd, *J*=13.80, 10.04Hz, 2 H) 1.93 - 2.06 (m, 1 H) 1.75 - 1.92 (m, 3 H) 1.63 - 1.72 (m, 1 H) 1.52 - 1.61 (m, 5 H) 1.38 - 1.50 (m, 3 H) 1.31 (s, 2 H) 1.13 (s, 9 H) 1.01 (dd, *J*=8.66, 6.90 Hz, 5 H) 0.79 - 0.94 (m, 2 H); MS: MS *m/z* 875.5 (M^++1).

Preparation of Compound 4088

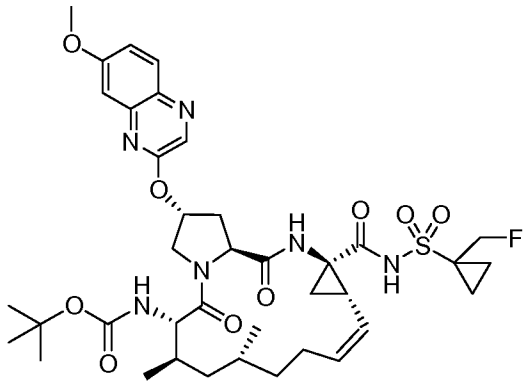


Compound 4088

Compound 4088 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4088: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(7-methoxyquinoxalin-2-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.08 (s, 1 H) 8.27 (s, 1 H) 7.85 - 7.93 (m, 1 H) 7.25 - 7.35 (m, 2 H) 5.90 (br. s., 1 H) 5.63 (d, *J*=5.77 Hz, 1 H) 4.72 - 4.81 (m, 2 H) 4.59 - 4.66 (m, 2 H) 4.09 (d, *J*=3.51 Hz, 1 H) 3.99 (s, 3 H) 3.81 (d, *J*=11.04 Hz, 1 H) 2.64 - 2.74 (m, 2 H) 2.34 - 2.53 (m, 2 H) 1.93 - 2.04 (m, 1 H) 1.82 - 1.92 (m, 1 H) 1.64 - 1.82 (m, 4 H) 1.59 (dd, *J*=9.54, 5.77 Hz, 1 H) 1.41 - 1.54 (m, 2 H) 1.16 - 1.33 (m, 11 H) 0.95 - 1.07 (m, 4 H) 0.77 - 0.93 (m, 2 H) ; MS: MS *m/z* 841.2 (M^++1).

Preparation of Compound 4089

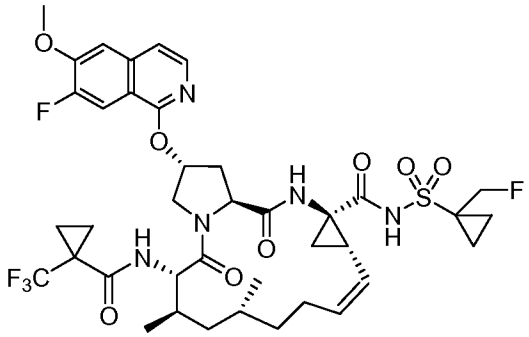


Compound 4089

Compound 4089 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4089: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(7-methoxyquinoxalin-2-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.07 (s, 1 H) 8.25 (s, 1 H) 7.83 - 7.93 (m, 1 H) 7.24 - 7.34 (m, 2 H) 5.92 (br. s., 1 H) 5.63 (td, *J*=10.42, 5.77 Hz, 1 H) 5.01 (t, *J*=10.04 Hz, 1 H) 4.65 - 4.74 (m, 1 H) 4.55 - 4.64 (m, 1 H) 4.10 (dd, *J*=11.80, 3.76 Hz, 1 H) 3.99 (s, 3 H) 3.84 (d, *J*=10.79 Hz, 1 H) 2.64 - 2.74 (m, 2 H) 2.34 - 2.54 (m, 2 H) 1.93 - 2.04 (m, 1 H) 1.78 - 1.91 (m, 2 H) 1.63 - 1.78 (m, 4 H) 1.59 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.42 - 1.55 (m, 2 H) 1.19 - 1.39 (m, 5 H) 1.15 (s, 10 H) 0.94 - 1.07 (m, 3 H) 0.78 - 0.93 (m, 2 H) ; MS: MS *m/z* 787.2 (M^++1).

Preparation of Compound 4090

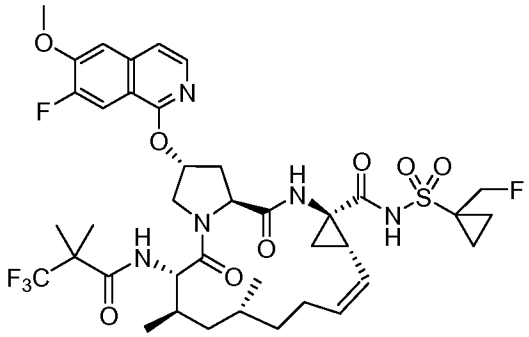


Compound 4090

Compound 4090 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4029.

Compound 4090: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-N-(1-(fluoromethyl)cyclopropylsulfonyl)-7,9-dimethyl-5,16-dioxo-6-(1-(trifluoromethyl)cyclopropanecarboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.99 (s, 1 H) 7.94 (d, *J*=6.02 Hz, 1 H) 7.77 (d, *J*=11.80 Hz, 1 H) 7.58 (d, *J*=7.78 Hz, 1 H) 7.41 (d, *J*=8.03 Hz, 1 H) 7.31 (d, *J*=5.52 Hz, 1 H) 5.90 (br. s., 1 H) 5.63 (d, *J*=5.52 Hz, 1 H) 5.02 (t, *J*=9.91 Hz, 1 H) 4.77 - 4.82 (m, 2 H) 4.48 - 4.66 (m, 3 H) 4.25 (dd, *J*=10.92, 8.41 Hz, 1 H) 4.02 - 4.09 (m, 4 H) 2.71 (d, *J*=9.03 Hz, 2 H) 2.39 - 2.49 (m, 2 H) 2.01 (d, *J*=4.77 Hz, 2 H) 1.81 - 1.89 (m, 1 H) 1.64 - 1.75 (m, 3 H) 1.46 - 1.61 (m, 3 H) 1.17 - 1.35 (m, 4 H) 1.08 - 1.16 (m, 3 H) 1.02 (dd, *J*=16.06, 6.78 Hz, 4 H) 0.83 - 0.98 (m, 1 H) ; MS: MS *m/z* 840.2 (M^++1).

Preparation of Compound 4091

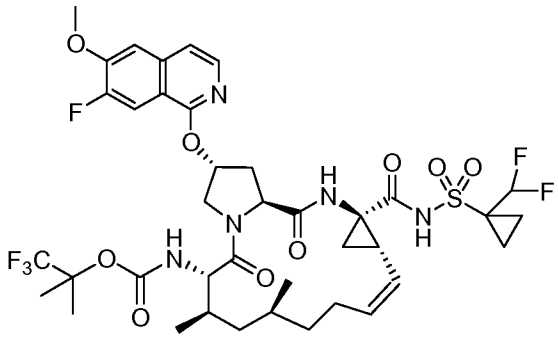


Compound 4091

Compound 4091 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4029.

Compound 4091: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-N-(1-(fluoromethyl)cyclopropylsulfonyl)-7,9-dimethyl-5,16-dioxo-6-(3,3,3-trifluoro-2,2-dimethylpropanamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.98 (s, 1 H) 7.94 (d, *J*=6.02 Hz, 1 H) 7.78 (d, *J*=11.80 Hz, 1 H) 7.60 (s, 1 H) 7.40 (d, *J*=8.28 Hz, 1 H) 7.31 (d, *J*=5.77 Hz, 1 H) 5.91 (s, 1 H) 5.64 (d, *J*=5.52 Hz, 1 H) 5.02 (t, *J*=10.16 Hz, 1 H) 4.77 - 4.82 (m, 2 H) 4.49 - 4.70 (m, 4 H) 4.27 (dd, *J*=10.79, 8.28 Hz, 1 H) 4.00 - 4.10 (m, 5 H) 3.43 (s, 1 H) 3.28 (dt, *J*=3.26, 1.63 Hz, 1 H) 2.73 (d, *J*=9.54 Hz, 3 H) 2.38 - 2.50 (m, 3 H) 1.94 - 2.14 (m, 2 H) 1.81 - 1.90 (m, 1 H) 1.64 - 1.76 (m, 4 H) 1.49 - 1.60 (m, 2 H) 1.17 - 1.34 (m, 5 H) 0.96 - 1.08 (m, 2 H) 0.88 (d, *J*=11.04 Hz, 1 H) ; MS: MS *m/z* 842.2 (M^++1).

Preparation of Compound 4092

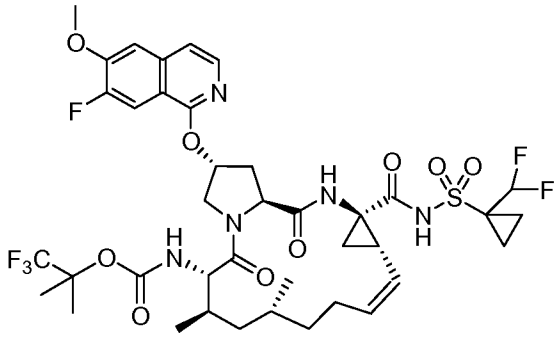


Compound 4092

Compound 4092 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4092: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(1-(difluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.94 (d, *J*=5.77 Hz, 1 H) 7.83 (d, *J*=11.54 Hz, 1 H) 7.39 (d, *J*=8.28 Hz, 1 H) 7.30 (d, *J*=5.77 Hz, 1 H) 7.25 (d, *J*=7.28 Hz, 1 H) 6.53 (s, 1 H) 5.89 (br. s., 1 H) 5.70 (br. s., 1 H) 5.03 - 5.20 (m, 1 H) 4.81 (s, 1 H) 4.66 - 4.73 (m, 1 H) 4.52 (d, *J*=11.80 Hz, 1 H) 4.06 - 4.22 (m, 2 H) 4.00 - 4.05 (m, 3 H) 3.66 (br. s., 1 H) 3.28 (br. s., 1 H) 2.63 - 2.78 (m, 1 H) 2.48 (br. s., 1 H) 2.01 (s, 2 H) 1.54 - 1.76 (m, 5 H) 1.43 - 1.53 (m, 5 H) 1.21 - 1.42 (m, 9 H) 1.12 (d, *J*=6.78 Hz, 1 H) 1.03 (d, *J*=7.28 Hz, 1 H) 0.93 (d, *J*=7.03 Hz, 3 H) ; MS: MS *m/z* 875.0 (M^+-1).

Preparation of Compound 4093

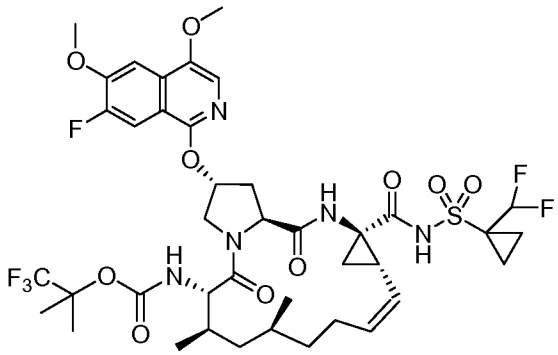


Compound 4093

Compound 4093 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4093: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(difluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.95 (d, *J*=5.77 Hz, 1 H) 7.79 (d, *J*=11.80 Hz, 1 H) 7.40 (d, *J*=8.28 Hz, 1 H) 7.30 (d, *J*=6.02 Hz, 2 H) 6.55 (s, 1 H) 5.89 (br. s., 1 H) 5.61 (d, *J*=6.27 Hz, 1 H) 5.07 (br. s., 1 H) 4.58 - 4.74 (m, 2 H) 3.97 - 4.07 (m, 4 H) 3.79 - 3.87 (m, 1 H) 3.29 (d, *J*=1.51 Hz, 1 H) 2.63 - 2.79 (m, 2 H) 2.34 - 2.52 (m, 2 H) 1.91 - 2.04 (m, 1 H) 1.78 - 1.90 (m, 2 H) 1.74 (dd, *J*=8.41, 5.65 Hz, 2 H) 1.60 (dd, *J*=9.54, 5.52 Hz, 2 H) 1.49 (d, *J*=13.30 Hz, 2 H) 1.22 - 1.42 (m, 6 H) 1.13 (s, 3 H) 1.01 (dd, *J*=9.29, 6.78 Hz, 5 H) 0.77 - 0.95 (m, 3 H) ; MS: MS *m/z* 874.9 (M^+-1).

Preparation of Compound 4094

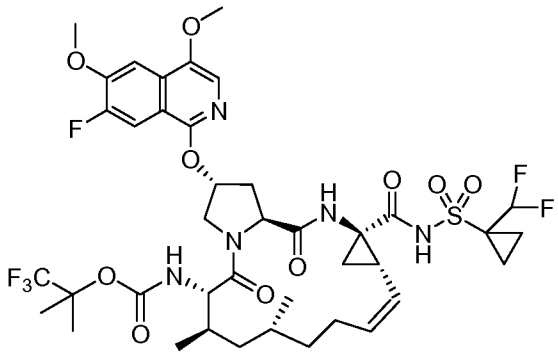


Compound 4094

Compound 4094 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4094: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(1-(difluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.78 (d, *J*=11.80 Hz, 1 H) 7.51 - 7.60 (m, 2 H) 5.81 (br. s., 1 H) 5.69 (br. s., 1 H) 5.04 - 5.21 (m, 1 H) 4.65 - 4.71 (m, 1 H) 4.48 (d, *J*=11.04 Hz, 1 H) 4.14 (d, *J*=6.53 Hz, 1 H) 4.00 - 4.10 (m, 8 H) 2.63 - 2.73 (m, 2 H) 2.45 (br. s., 2 H) 2.01 (s, 2 H) 1.70 (d, *J*=7.28 Hz, 2 H) 1.49 (s, 2 H) 1.29 - 1.40 (m, 10 H) 1.18 - 1.28 (m, 4 H) 1.12 (d, *J*=6.78 Hz, 3 H) 0.93 (d, *J*=6.78 Hz, 3 H) ; MS: MS *m/z* 905.0 (M^+-1).

Preparation of Compound 4095

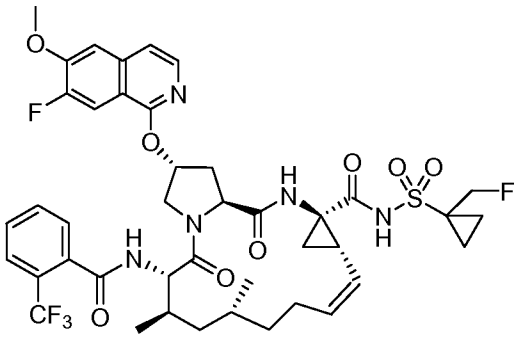


Compound 4095

Compound 4095 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4095: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(difluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.75 (d, *J*=11.54 Hz, 1 H) 7.53 - 7.60 (m, 2 H) 5.81 (br. s., 1 H) 5.56 - 5.66 (m, 1 H) 5.00 - 5.19 (m, 1 H) 4.57 - 4.71 (m, 2 H) 3.96 - 4.07 (m, 7 H) 3.82 (d, *J*=10.79 Hz, 1 H) 3.28 (br. s., 1 H) 2.72 (dd, *J*=12.92, 7.40 Hz, 2 H) 2.35 - 2.48 (m, 2 H) 2.01 (s, 1 H) 1.77 - 1.91 (m, 2 H) 1.73 (dd, *J*=8.28, 5.52 Hz, 2 H) 1.60 (d, *J*=9.29 Hz, 2 H) 1.49 (d, *J*=11.54 Hz, 2 H) 1.30 - 1.44 (m, 7 H) 1.26 (d, *J*=9.54 Hz, 2 H) 1.14 (s, 3 H) 1.01 (dd, *J*=10.67, 6.65 Hz, 4 H) 0.77 - 0.95 (m, 1 H) ; MS: MS *m/z* 906.6 (M^++1).

Preparation of Compound 4086

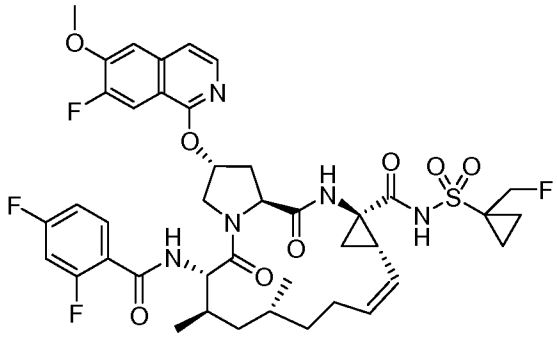


Compound 4096

Compound 4096 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4029.

Compound 4096: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-N-(1-(fluoromethyl)cyclopropylsulfonyl)-7,9-dimethyl-5,16-dioxo-6-(2-(trifluoromethyl)benzamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.02 (s, 1 H) 8.78 (d, *J*=9.03 Hz, 1 H) 7.92 (d, *J*=5.77 Hz, 2 H) 7.82 (d, *J*=11.54 Hz, 1 H) 7.68 (dd, *J*=5.52, 3.76 Hz, 1 H) 7.55 - 7.62 (m, 2 H) 7.25 - 7.36 (m, 3 H) 5.99 (br. s., 1 H) 5.59 - 5.67 (m, 1 H) 5.00 (t, *J*=10.04 Hz, 1 H) 4.61 - 4.73 (m, 3 H) 4.44 - 4.55 (m, 2 H) 4.19 (dd, *J*=11.42, 3.64 Hz, 1 H) 4.01 (s, 3 H) 3.29 (dd, *J*=3.26, 1.51 Hz, 1 H) 2.68 - 2.80 (m, 3 H) 2.47 (ddd, *J*=14.05, 10.04, 4.27 Hz, 2 H) 1.95 - 2.15 (m, 2 H) 1.90 (dd, *J*=13.93, 5.65 Hz, 1 H) 1.63 - 1.77 (m, 3 H) 1.47 - 1.62 (m, 2 H) 1.16 - 1.36 (m, 3 H) 1.07 (dd, *J*=9.54, 6.53 Hz, 4 H) 0.94 (t, *J*=12.30 Hz, 1 H) ; MS: MS *m/z* 876.4 (M^++1).

Preparation of Compound 4097

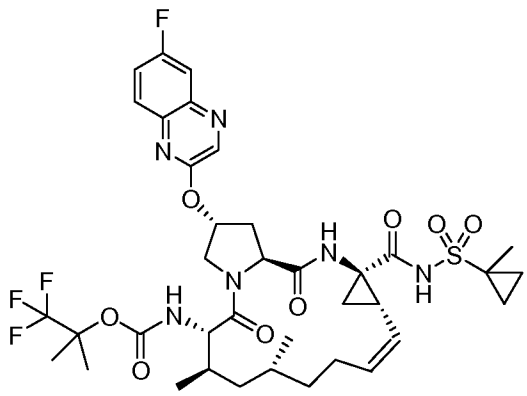


Compound 4097

Compound 4097 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4029.

Compound 4097: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(2,4-difluorobenzamido)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-N-(1-(fluoromethyl)cyclopropylsulfonyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.13 - 8.19 (m, 1 H) 7.94 (d, *J*=6.02 Hz, 1 H) 7.81 (d, *J*=11.54 Hz, 1 H) 7.41 (q, *J*=8.03 Hz, 1 H) 5.94 (br. s., 1 H) 5.62 (td, *J*=9.98, 6.15 Hz, 1 H) 5.01 (t, *J*=10.04 Hz, 1 H) 4.79 (dd, *J*=11.42, 6.90 Hz, 2 H) 4.59 - 4.66 (m, 2 H) 4.38 - 4.44 (m, 1 H) 4.10 (dd, *J*=11.54, 3.26 Hz, 1 H) 4.03 (s, 4 H) 3.28 (dt, *J*=3.26, 1.63 Hz, 1 H) 2.65 - 2.80 (m, 3 H) 2.46 (ddd, *J*=13.80, 10.04, 4.02 Hz, 3 H) 1.96 - 2.13 (m, 2 H) 1.82 - 1.90 (m, 1 H) 1.64 - 1.75 (m, 3 H) 1.46 - 1.60 (m, 3 H) 1.17 - 1.34 (m, 3 H) 1.06 (dd, *J*=6.40, 5.40 Hz, 6 H) 0.93 (s, 1 H) ; MS: MS *m/z* 842.2 (M^+-1).

Preparation of Compound 4099

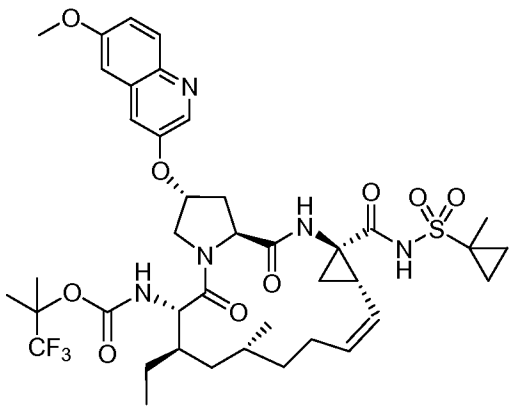


Compound 4099

Compound 4099 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4099: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(6-fluoroquinoxalin-2-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.97 (dd, *J*=9.03, 5.52 Hz, 1 H) 7.92 (s, 1 H) 7.57 - 7.72 (m, 1 H) 7.34 (d, *J*=8.28 Hz, 1 H) 5.89 (br. s., 1 H) 5.63 (d, *J*=5.52 Hz, 1 H) 5.02 (t, *J*=9.91 Hz, 1 H) 4.73 - 4.81 (m, 2 H) 4.63 (dd, *J*=9.79, 7.28 Hz, 1 H) 4.07 (dd, *J*=11.92, 3.39 Hz, 1 H) 3.79 (dd, *J*=10.67, 8.16 Hz, 1 H) 3.25 - 3.29 (m, 2 H) 2.66 - 2.77 (m, 2 H) 2.35 - 2.53 (m, 2 H) 1.98 (br. s., 1 H) 1.88 (d, *J*=5.77 Hz, 1 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 2 H) 1.63 - 1.72 (m, 1 H) 1.59 (dd, *J*=8.78, 6.53 Hz, 1 H) 1.39 - 1.55 (m, 7 H) 1.17 - 1.36 (m, 8 H) 0.94 - 1.05 (m, 3 H) 0.79 - 0.93 (m, 1 H) ; MS: MS *m/z* 811.4 (M^++1).

Preparation of Compound 4100

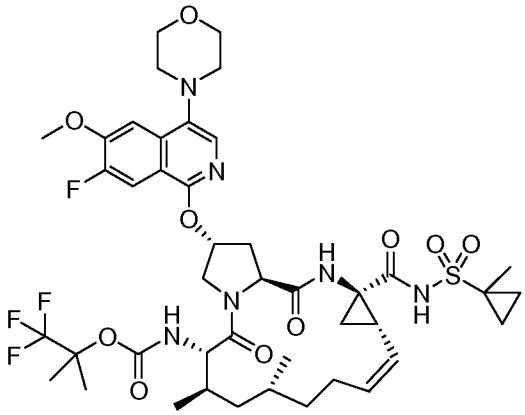


Compound 4100

Compound 4100 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4100: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(6-methoxyquinolin-3-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.37 (d, *J*=2.76 Hz, 1 H) 7.84 (d, *J*=9.03 Hz, 1 H) 7.75 (d, *J*=2.76 Hz, 1 H) 7.23 - 7.31 (m, 2 H) 5.62 (br. s., 1 H) 5.39 (br. s., 1 H) 5.02 (br. s., 1 H) 4.71 (d, *J*=12.30 Hz, 1 H) 4.57 - 4.63 (m, 1 H) 4.02 - 4.12 (m, 2 H) 3.97 (s, 3 H) 2.70 (d, *J*=6.27 Hz, 2 H) 2.44 (d, *J*=10.29 Hz, 2 H) 1.95 - 2.07 (m, 2 H) 1.76 (d, *J*=7.53 Hz, 1 H) 1.50 - 1.62 (m, 8 H) 1.43 (d, *J*=10.79 Hz, 2 H) 1.30 - 1.38 (m, 5 H) 1.13 (s, 3 H) 1.01 (d, *J*=6.53 Hz, 3 H) 0.88 - 0.95 (m, 3 H) 0.82 (t, *J*=7.53 Hz, 3 H)
MS: MS *m/z* 836.93 (M^++1).

Preparation of Compound 4101

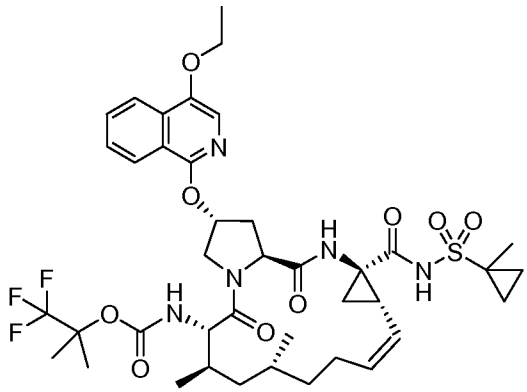


Compound 4101

Compound 4101 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4101: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-6-methoxy-4-morpholinoisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.04 (s, 1 H) 7.71 - 7.82 (m, 2 H) 7.60 (d, *J*=8.53 Hz, 1 H) 5.83 - 5.88 (m, 1 H) 5.63 (d, *J*=5.77 Hz, 1 H) 5.01 (t, *J*=10.04 Hz, 1 H) 4.61 - 4.73 (m, 2 H) 4.01 - 4.09 (m, 4 H) 3.91 - 4.01 (m, 4 H) 3.82 (d, *J*=10.79 Hz, 1 H) 3.03 - 3.13 (m, 4 H) 2.67 - 2.79 (m, 2 H) 2.36 - 2.49 (m, 2 H) 1.87 - 2.02 (m, 2 H) 1.71 - 1.86 (m, 2 H) 1.61 - 1.70 (m, 1 H) 1.48 - 1.61 (m, 5 H) 1.35 - 1.47 (m, 5 H) 1.19 - 1.34 (m, 2 H) 1.13 (s, 3 H) 1.01 (t, *J*=6.40 Hz, 6 H) 0.79 - 0.95 (m, 3 H) ; MS: MS *m/z* 926.4 (M^++1).

Preparation of Compound 4102

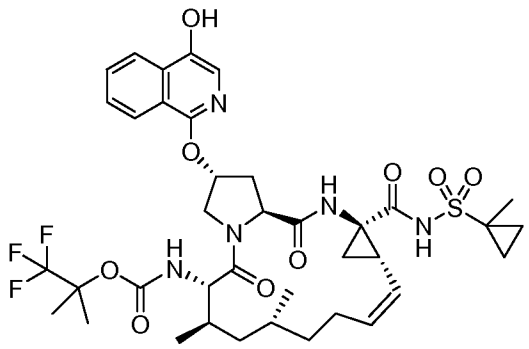


Compound 4102

Compound 4102 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4102: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.09 (dd, *J*=17.19, 8.16 Hz, 2 H) 7.75 - 7.83 (m, 2 H) 7.59 - 7.66 (m, 1 H) 5.84 (br. s., 1 H) 5.72 (br. s., 1 H) 5.00 (br. s., 1 H) 4.38 (t, *J*=8.53 Hz, 1 H) 4.21 (d, *J*=7.28 Hz, 2 H) 4.13 (br. s., 1 H) 3.90 - 3.98 (m, 1 H) 2.43 - 2.48 (m, 1 H) 1.92 (br. s., 1 H) 1.57 (br. s., 2 H) 1.39 - 1.54 (m, 10 H) 1.34 (br. s., 5 H) 1.25 (br. s., 4 H) 1.02 - 1.11 (m, 4 H) 0.82 - 0.96 (m, 10 H) 0.76 (d, *J*=9.29 Hz, 1 H) ; MS: MS *m/z* 838.6 (M^++1).

Preparation of Compound 4103

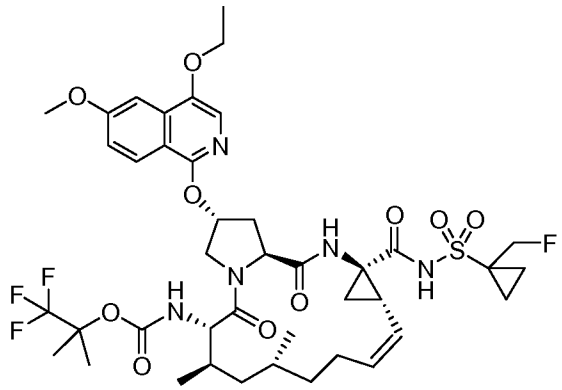


Compound 4103

Compound 4103 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4103: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-hydroxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 11.04 (s, 1 H) 9.76 (s, 1 H) 9.13 (s, 1 H) 8.06 (d, *J*=9.29 Hz, 2 H) 7.71 - 7.85 (m, 2 H) 7.58 (d, *J*=8.03 Hz, 1 H) 7.55 (s, 1 H) 5.71 - 5.78 (m, 1 H) 5.74 (br. s., 1 H) 5.49 - 5.58 (m, 1 H) 5.48 - 5.58 (m, 1 H) 4.96 (t, *J*=10.04 Hz, 1 H) 4.47 - 4.56 (m, 2 H) 3.86 - 3.93 (m, 1 H) 3.71 (dd, *J*=10.54, 8.28 Hz, 1 H) 2.56 - 2.75 (m, 2 H) 2.23 - 2.40 (m, 2 H) 1.76 - 1.95 (m, 2 H) 1.60 - 1.75 (m, 2 H) 1.39 - 1.58 (m, 6 H) 1.22 - 1.38 (m, 5 H) 1.04 - 1.21 (m, 4 H) 0.91 (dd, *J*=17.44, 6.90 Hz, 6 H) 0.75 (t, *J*=12.17 Hz, 1 H) ; MS: MS *m/z* 808.5 (M^++1).

Preparation of Compound 4104

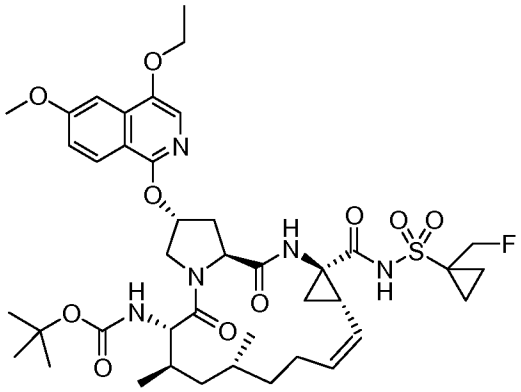


Compound 4104

Compound 4104 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4104: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxy-6-methoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.03 (s, 1 H) 8.07 (d, *J*=9.03 Hz, 1 H) 7.52 (s, 1 H) 7.45 (d, *J*=2.51 Hz, 1 H) 7.14 (dd, *J*=9.29, 2.51 Hz, 1 H) 5.80 (br. s., 1 H) 5.62 (td, *J*=10.35, 5.90 Hz, 1 H) 4.95 - 5.04 (m, 1 H) 4.76 - 4.82 (m, 1 H) 4.71 (d, *J*=11.54 Hz, 1 H) 4.59 - 4.67 (m, 2 H) 4.24 (q, *J*=6.86 Hz, 2 H) 4.01 (dd, *J*=11.54, 3.51 Hz, 1 H) 3.96 (s, 3 H) 3.81 - 3.88 (m, 1 H) 3.28 (dt, *J*=3.39, 1.57 Hz, 1 H) 2.67 - 2.75 (m, 2 H) 2.37 - 2.48 (m, 2 H) 1.86 - 2.03 (m, 2 H) 1.77 - 1.85 (m, 1 H) 1.64 - 1.76 (m, 3 H) 1.44 - 1.63 (m, 5 H) 1.35 - 1.43 (m, 3 H) 1.17 - 1.34 (m, 3 H) 0.96 - 1.07 (m, 9 H) 0.83 (t, *J*=11.67 Hz, 1 H) ; MS: MS *m/z* 884.5 (M^++1).

Preparation of Compound 4105

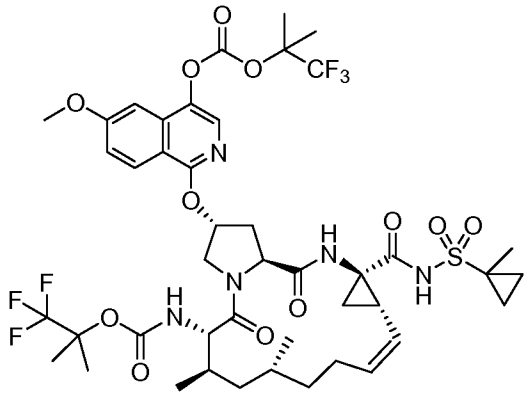


Compound 4105

Compound 4105 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4105: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxy-6-methoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.07 (d, *J*=9.29 Hz, 1 H) 7.51 (s, 1 H) 7.43 (d, *J*=2.51 Hz, 1 H) 7.13 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.81 (br. s., 1 H) 5.58 - 5.66 (m, 1 H) 5.00 (t, *J*=9.91 Hz, 1 H) 4.79 (d, *J*=11.29 Hz, 1 H) 4.64 - 4.71 (m, 1 H) 4.56 - 4.63 (m, 1 H) 4.52 (d, *J*=11.04 Hz, 1 H) 4.23 (q, *J*=7.03 Hz, 2 H) 4.03 (dd, *J*=11.54, 3.51 Hz, 1 H) 3.96 (s, 3 H) 3.85 - 3.92 (m, 1 H) 3.29 (d, *J*=1.76 Hz, 1 H) 2.67 - 2.76 (m, 2 H) 2.37 - 2.48 (m, 2 H) 1.97 (br. s., 1 H) 1.77 - 1.92 (m, 2 H) 1.62 - 1.76 (m, 3 H) 1.47 - 1.60 (m, 6 H) 1.30 - 1.46 (m, 1 H) 1.11 - 1.29 (m, 9 H) 1.01 (dd, *J*=13.93, 6.65 Hz, 6 H) 0.84 (t, *J*=11.54 Hz, 3 H) ; MS: MS *m/z* 830.2 (M^++1).

Preparation of Compound 4106

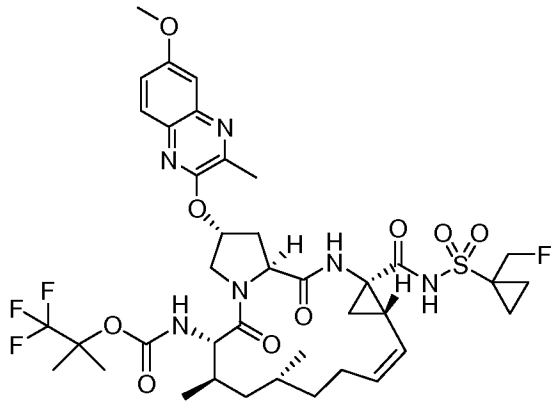


Compound 4106

Compound 4106 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4106: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(6-methoxy-4-((1,1,1-trifluoro-2-methylpropan-2-yloxy)carbonyloxy)isoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.16 (d, *J*=9.03 Hz, 1 H) 7.94 (s, 1 H) 7.30 (d, *J*=7.78 Hz, 1 H) 7.21 (dd, *J*=9.16, 2.38 Hz, 1 H) 7.05 (d, *J*=2.51 Hz, 1 H) 5.91 (br. s., 1 H) 5.63 (d, *J*=6.02 Hz, 1 H) 5.02 (t, *J*=10.16 Hz, 1 H) 4.76 - 4.82 (m, 3 H) 4.64 - 4.70 (m, 1 H) 4.03 (d, *J*=7.78 Hz, 1 H) 3.96 (s, 4 H) 3.80 - 3.87 (m, 1 H) 3.28 (br. s., 2 H) 2.69 - 2.81 (m, 3 H) 2.40 - 2.50 (m, 2 H) 1.98 (br. s., 1 H) 1.86 - 1.93 (m, 1 H) 1.76 - 1.86 (m, 5 H) 1.67 (d, *J*=9.29 Hz, 1 H) 1.50 - 1.61 (m, 4 H) 1.40 - 1.49 (m, 3 H) 1.29 - 1.40 (m, 3 H) 1.26 (br. s., 1 H) 0.96 - 1.06 (m, 6 H) 0.86 - 0.95 (m, 2 H) 0.79 - 0.86 (m, 1 H) ; MS: MS *m/z* 992.6 (M^++1).

Preparation of Compound 4107

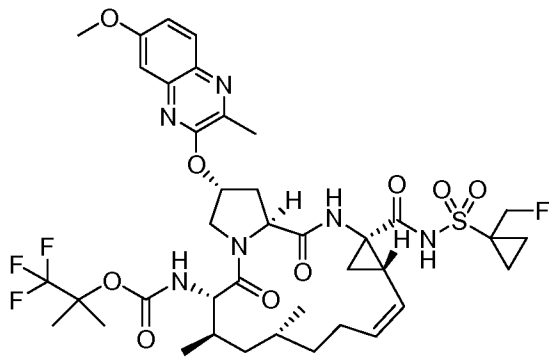


Compound 4107

Compound 4107 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 107: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(6-methoxy-3-methylquinoxalin-2-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.78 (d, *J*=9.03 Hz, 1 H) 7.31 - 7.37 (m, 2 H) 5.88 (br. s., 1 H) 5.63 (td, *J*=10.10, 5.90 Hz, 1 H) 5.01 (t, *J*=9.79 Hz, 1 H) 4.89 - 4.94 (m, 2 H) 4.77 - 4.82 (m, 1 H) 4.71 (s, 1 H) 4.60 - 4.68 (m, 1 H) 4.04 (dd, *J*=11.67, 3.39 Hz, 1 H) 3.95 (s, 3 H) 3.74 - 3.80 (m, 1 H) 3.37 - 3.44 (m, 2 H) 3.28 (dt, *J*=3.26, 1.63 Hz, 1 H) 2.70 (q, *J*=9.20 Hz, 2 H) 2.57 (s, 3 H) 2.39 - 2.52 (m, 2 H) 1.96 (br. s., 1 H) 1.81 (dd, *J*=13.30, 5.52 Hz, 1 H) 1.64 - 1.76 (m, 3 H) 1.59 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.48 (br. s., 2 H) 1.16 - 1.34 (m, 9 H) 1.00 (dd, *J*=19.32, 6.78 Hz, 5 H) 0.79 - 0.88 (m, 1 H) ; MS: MS *m/z* 855.5 (M^++1).

Preparation of Compound 4108

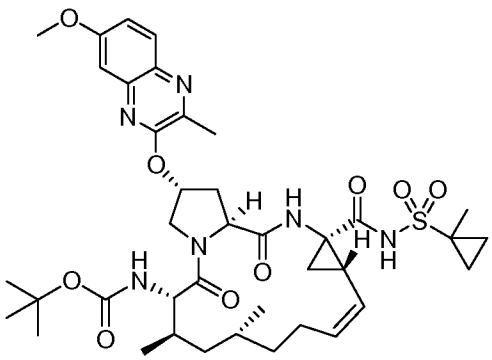


Compound 4108

Compound 4108 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4108: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(7-methoxy-3-methylquinoxalin-2-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.08 (s, 1 H) 7.79 (d, *J*=8.53 Hz, 1 H) 7.21 - 7.33 (m, 2 H) 5.91 (br. s., 1 H) 5.63 (d, *J*=5.02 Hz, 1 H) 5.01 (t, *J*=10.04 Hz, 1 H) 4.92 (d, *J*=11.04 Hz, 1 H) 4.77 (dd, *J*=18.57, 11.29 Hz, 2 H) 4.64 (d, *J*=10.29 Hz, 2 H) 4.52 (d, *J*=11.29 Hz, 1 H) 4.06 (d, *J*=12.05 Hz, 1 H) 3.97 (s, 4 H) 3.77 (d, *J*=10.54 Hz, 1 H) 2.64 - 2.77 (m, 2 H) 2.35 - 2.58 (m, 7 H) 1.96 (br. s., 1 H) 1.77 - 1.90 (m, 1 H) 1.63 - 1.76 (m, 2 H) 1.59 (d, *J*=8.03 Hz, 2 H) 1.49 (br. s., 2 H) 1.16 - 1.42 (m, 9 H) 1.01 (dd, *J*=18.70, 6.15 Hz, 3 H) 0.84 (t, *J*=12.80 Hz, 1 H) ; MS: MS *m/z* 855.5 (M^++1).

Preparation of Compound 4109

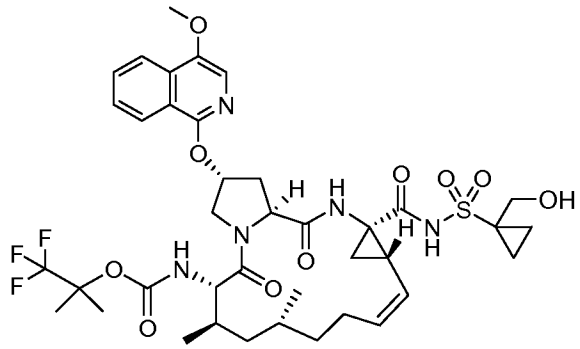


Compound 4109

Compound 4109 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4109: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-methoxy-3-methylquinoxalin-2-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.78 (d, *J*=9.03 Hz, 1 H) 7.30 (d, *J*=2.51 Hz, 1 H) 7.23 (dd, *J*=9.29, 2.76 Hz, 1 H) 6.66 (d, *J*=7.28 Hz, 1 H) 5.94 (br. s., 1 H) 5.59 - 5.67 (m, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.90 - 4.97 (m, 2 H) 4.70 - 4.81 (m, 2 H) 4.60 - 4.67 (m, 1 H) 4.08 (d, *J*=8.28 Hz, 1 H) 3.97 (s, 4 H) 3.77 - 3.85 (m, 1 H) 3.29 (dd, *J*=3.26, 1.51 Hz, 2 H) 2.67 - 2.78 (m, 2 H) 2.41 - 2.58 (m, 5 H) 1.98 (br. s., 1 H) 1.75 - 1.90 (m, 3 H) 1.64 - 1.74 (m, 1 H) 1.58 (dd, *J*=9.54, 5.77 Hz, 1 H) 1.41 - 1.56 (m, 4 H) 1.21 - 1.38 (m, 3 H) 1.08 - 1.21 (m, 7 H) 1.00 (dd, *J*=14.43, 6.65 Hz, 2 H) 0.80 - 0.92 (m, 1H) ; MS: MS *m/z* 783.5 (M^++1).

Preparation of Compound 4110

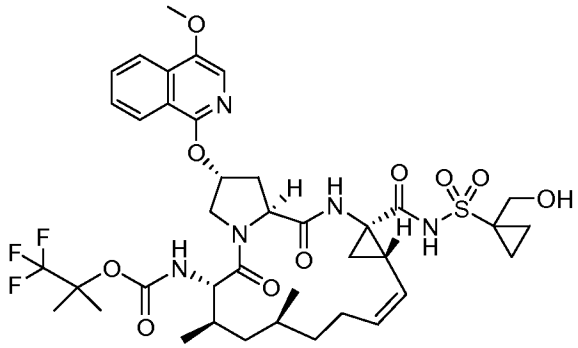


Compound 4110

Compound 4110 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4110: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(hydroxymethyl)cyclopropylsulfonylcarbamoyl)-2-(4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.11 - 8.20 (m, 2 H) 7.72 - 7.77 (m, 1 H) 7.55 - 7.60 (m, 2 H) 5.83 (br. s., 1 H) 5.58 (td, *J*=10.35, 5.14 Hz, 1 H) 5.36 - 5.43 (m, 1 H) 4.71 (d, *J*=11.54 Hz, 1 H) 4.52 - 4.63 (m, 2 H) 4.39 (d, *J*=12.30 Hz, 1 H) 3.98 - 4.05 (m, 2 H) 3.84 (d, *J*=10.79 Hz, 1 H) 3.28 (br. s., 1 H) 2.70 (dd, *J*=13.80, 7.28 Hz, 1 H) 2.60 (q, *J*=9.37 Hz, 1 H) 2.35 - 2.53 (m, 2 H) 1.82 - 1.97 (m, 3 H) 1.66 - 1.74 (m, 2 H) 1.35 - 1.46 (m, 9 H) 1.15 - 1.34 (m, 4 H) 1.05 - 1.14 (m, 1 H) 0.94 - 1.05 (m, 7 H) 0.73 - 0.83 (m, 3 H) ; MS: MS *m/z* 838.2 (M^++1).

Preparation of Compound 4111

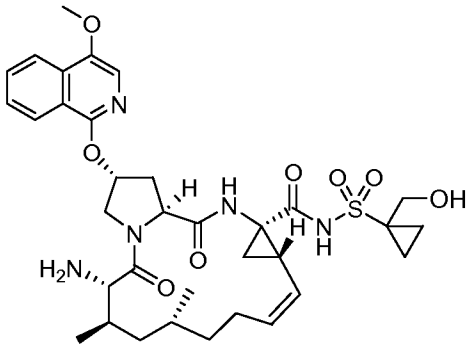


Compound 4111

Compound 4111 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4111: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(1-(hydroxymethyl)cyclopropylsulfonylcarbamoyl)-2-(4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.10 - 8.22 (m, 2 H) 7.75 (t, *J*=7.65 Hz, 1 H) 7.55 - 7.62 (m, 2 H) 5.83 (br. s., 1 H) 5.65 - 5.74 (m, 1 H) 5.36 (t, *J*=9.54 Hz, 1 H) 4.73 (t, *J*=8.16 Hz, 1 H) 4.48 - 4.56 (m, 2 H) 4.36 - 4.43 (m, 1 H) 4.07 - 4.18 (m, 2 H) 4.03 (s, 3 H) 2.63 - 2.72 (m, 1 H) 2.49 - 2.58 (m, 2 H) 2.39 (q, *J*=9.03 Hz, 1 H) 1.89 - 2.09 (m, 3 H) 1.55 - 1.73 (m, 3 H) 1.36 - 1.49 (m, 7 H) 1.15 - 1.33 (m, 7 H) 0.97 - 1.14 (m, 5 H) 0.90 (d, *J*=6.78 Hz, 3 H) ; MS: MS *m/z* 838.2 (M^++1).

Preparation of Compound 4112

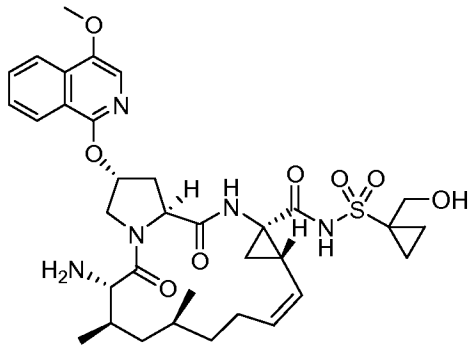


Compound 4112

Compound 4112 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4112: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(1-(hydroxymethyl)cyclopropylsulfonyl)-2-(4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.10 - 8.26 (m, 2 H) 7.77 (ddd, *J*=8.28, 7.03, 1.25 Hz, 1 H) 7.57 - 7.67 (m, 2 H) 5.88 (d, *J*=2.26 Hz, 1 H) 5.58 (td, *J*=10.60, 4.89 Hz, 1 H) 5.38 (t, *J*=10.29 Hz, 1 H) 4.52 - 4.64 (m, 2 H) 4.35 (d, *J*=12.30 Hz, 1 H) 4.10 - 4.21 (m, 2 H) 4.03 (s, 3 H) 3.36 - 3.43 (m, 1 H) 2.41 - 2.71 (m, 4 H) 1.77 - 2.03 (m, 5 H) 1.71 (ddd, *J*=17.00, 9.22, 5.14 Hz, 3 H) 1.36 - 1.51 (m, 3 H) 1.14 - 1.34 (m, 3 H) 0.98 - 1.12 (m, 7 H) 0.79 - 0.91 (m, 1 H) ; MS: MS *m/z* 684.5 (M^++1).

Preparation of Compound 4113

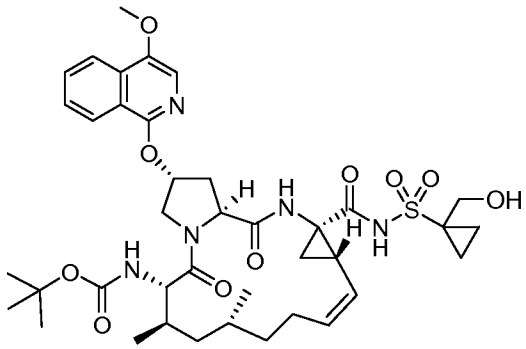


Compound 4113

Compound 4113 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4113: (2R,6S,7R,9S,13aS,14aR,16aS,Z)-6-amino-N-(1-(hydroxymethyl)cyclopropylsulfonyl)-2-(4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.15 (t, *J*=7.78 Hz, 2 H) 7.92 (s, 1 H) 7.74 - 7.79 (m, 1 H) 7.59 - 7.65 (m, 2 H) 5.88 (br. s., 1 H) 5.75 - 5.83 (m, 1 H) 5.32 (t, *J*=9.66 Hz, 1 H) 4.74 - 4.81 (m, 1 H) 4.49 - 4.55 (m, 1 H) 4.37 - 4.43 (m, 1 H) 4.11 - 4.23 (m, 2 H) 3.97 - 4.05 (m, 4 H) 3.29 (d, *J*=1.51 Hz, 1 H) 2.65 - 2.79 (m, 2 H) 2.49 - 2.58 (m, 1 H) 2.28 (q, *J*=8.45 Hz, 1 H) 1.87 - 1.99 (m, 4 H) 1.59 - 1.73 (m, 3 H) 1.34 - 1.46 (m, 4 H) 1.25 - 1.33 (m, 4 H) 1.14 - 1.24 (m, 2 H) 1.01 - 1.13 (m, 2 H) 0.87 - 1.00 (m, 3 H) ; MS: MS *m/z* 684.5 (M^++1).

Preparation of Compound 4114

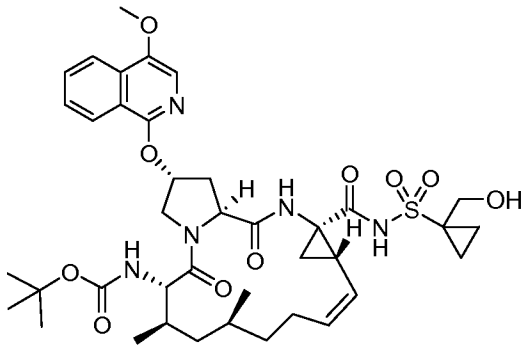


Compound 4114

Compound 4114 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4114: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(hydroxymethyl)cyclopropylsulfonylcarbamoyl)-2-(4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.09 - 8.21 (m, 2 H) 7.73 (t, *J*=7.65 Hz, 1 H) 7.53 - 7.60 (m, 2 H) 5.84 (br. s., 1 H) 5.58 (td, *J*=10.29, 5.02 Hz, 1 H) 5.39 (t, *J*=10.16 Hz, 1 H) 4.67 (d, *J*=11.04 Hz, 1 H) 4.50 - 4.61 (m, 2 H) 4.38 (d, *J*=12.55 Hz, 1 H) 4.00 - 4.08 (m, 5 H) 3.90 (d, *J*=10.79 Hz, 1 H) 3.79 - 3.93 (m, 2 H) 3.06 (q, *J*=7.28 Hz, 1 H) 2.57 - 2.74 (m, 2 H) 2.35 - 2.53 (m, 2 H) 1.78 - 2.00 (m, 3 H) 1.69 (dd, *J*=9.03, 2.51 Hz, 2 H) 1.37 - 1.51 (m, 4 H) 1.22 - 1.36 (m, 3 H) 1.06 - 1.21 (m, 9 H) 0.94 - 1.05 (m, 5 H) 0.74 - 0.84 (m, 1 H) ; MS: MS *m/z* 784.5 (M^++1).

Preparation of Compound 4115

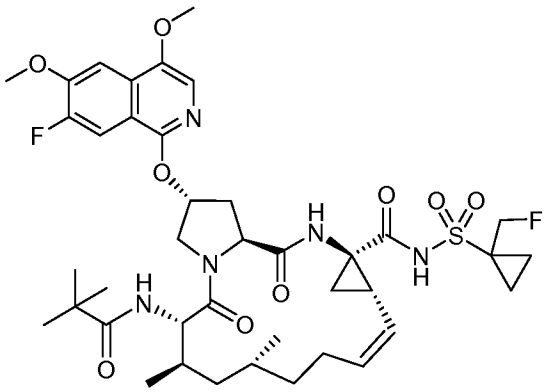


Compound 4115

Compound 4115 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4115: tert-butyl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(1-(hydroxymethyl)cyclopropylsulfonylcarbamoyl)-2-(4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.09 - 8.19 (m, 2 H) 7.73 (t, *J*=7.53 Hz, 1 H) 7.51 - 7.59 (m, 2 H) 5.83 (br. s., 1 H) 5.59 (s, 1 H) 4.89 - 4.98 (m, 2 H) 4.56 - 4.73 (m, 2 H) 3.99 - 4.07 (m, 4 H) 3.81 - 3.93 (m, 2 H) 3.29 (d, *J*=1.76 Hz, 2 H) 2.72 (s, 1 H) 2.36 - 2.54 (m, 2 H) 1.97 (br. s., 1 H) 1.85 (br. s., 2 H) 1.71 (br. s., 1 H) 1.47 (br. s., 5 H) 1.20 - 1.36 (m, 3 H) 1.08 - 1.18 (m, 9 H) 1.01 (dd, *J*=13.93, 6.65 Hz, 7 H) 0.93 (s, 1 H) 0.76 - 0.86 (m, 1 H) ; MS: MS *m/z* 784.5 (M^+-1).

Preparation of Compound 4116

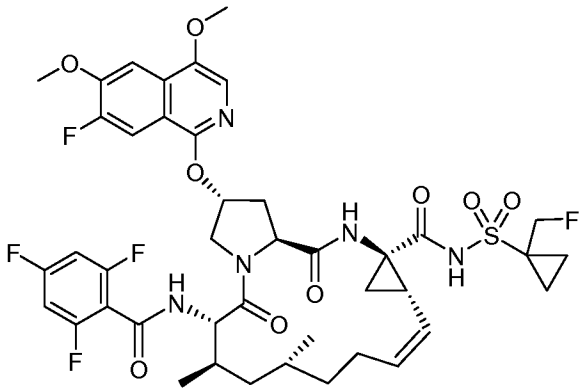


Compound 4116

Compound 4116 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4015.

Compound 4116: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-N-(1-(fluoromethyl)cyclopropylsulfonyl)-7,9-dimethyl-5,16-dioxo-6-pivalamido-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.98 (s, 1 H) 7.72 (d, *J*=11.54 Hz, 1 H) 7.52 - 7.59 (m, 2 H) 7.22 (d, *J*=9.54 Hz, 1 H) 5.84 (br. s., 1 H) 5.60 - 5.68 (m, 1 H) 5.01 (t, *J*=9.91 Hz, 1 H) 4.89 - 4.95 (m, 2 H) 4.76 - 4.82 (m, 2 H) 4.49 - 4.67 (m, 3 H) 4.27 (dd, *J*=11.04, 8.78 Hz, 1 H) 4.01 - 4.08 (m, 7 H) 3.25 - 3.30 (m, 2 H) 2.67 - 2.78 (m, 2 H) 2.37 - 2.47 (m, 2 H) 2.02 (br. s., 2 H) 1.79 - 1.88 (m, 1 H) 1.65 - 1.76 (m, 3 H) 1.45 - 1.62 (m, 3 H) 1.16 - 1.34 (m, 4 H) 0.94 - 1.07 (m, 9 H) 0.83 - 0.91 (m, 2 H) ; MS: MS *m/z* 818.4 (M^++1).

Preparation of Compound 4117

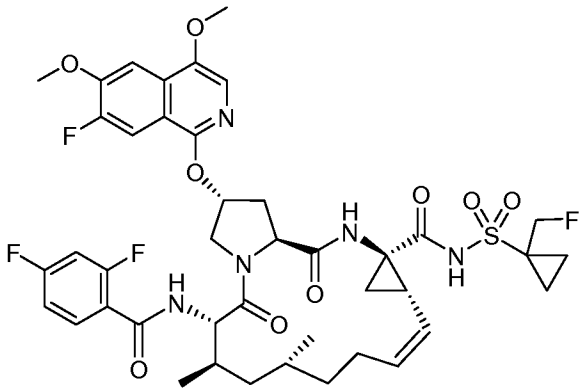


Compound 4117

Compound 4117 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4029.

Compound 4117: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-N-(1-(fluoromethyl)cyclopropylsulfonyl)-7,9-dimethyl-5,16-dioxo-6-(2,4,6-trifluorobenzamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.97 - 9.04 (m, 2 H) 7.75 (d, *J*=11.80 Hz, 1 H) 7.50 - 7.55 (m, 2 H) 6.87 (dd, *J*=9.03, 7.53 Hz, 2 H) 5.87 (br. s., 1 H) 5.63 (td, *J*=10.16, 6.02 Hz, 1 H) 4.95 - 5.04 (m, 2 H) 4.64 - 4.73 (m, 2 H) 4.42 - 4.63 (m, 4 H) 4.13 (dd, *J*=11.54, 3.76 Hz, 1 H) 4.01 (s, 6 H) 2.69 - 2.79 (m, 2 H) 2.37 - 2.47 (m, 2 H) 1.97 - 2.12 (m, 2 H) 1.82 - 1.90 (m, 1 H) 1.64 - 1.74 (m, 3 H) 1.45 - 1.60 (m, 4 H) 1.18 - 1.33 (m, 4 H) 1.07 (t, *J*=6.53 Hz, 6 H) 0.87 - 0.96 (m, 1 H) ; MS: MS *m/z* 893.2 (M^++1).

Preparation of Compound 4118

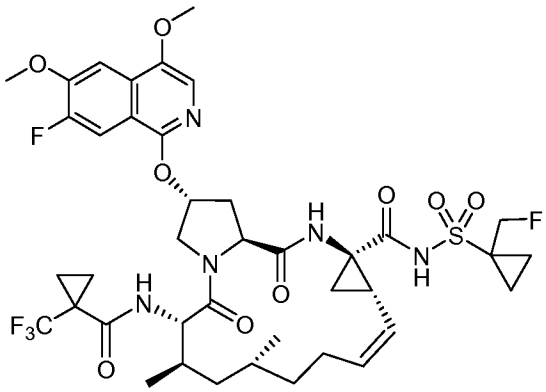


Compound 4118

Compound 4118 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4029.

Compound 4118: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(2,4-difluorobenzamido)-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-N-(1-(fluoromethyl)cyclopropylsulfonyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.02 (s, 1 H) 8.13 (br. s., 1 H) 7.92 (s, 1 H) 7.74 (d, *J*=11.80 Hz, 1 H) 7.49 - 7.55 (m, 1 H) 7.33 - 7.41 (m, 1 H) 6.90 - 7.02 (m, 2 H) 5.85 (s, 1 H) 5.63 (d, *J*=6.02 Hz, 1 H) 5.02 (t, *J*=10.29 Hz, 1 H) 4.72 (d, *J*=11.29 Hz, 1 H) 4.59 - 4.68 (m, 2 H) 4.38 - 4.45 (m, 1 H) 4.00 - 4.10 (m, 8 H) 3.25 - 3.30 (m, 1 H) 2.67 - 2.78 (m, 3 H) 2.39 - 2.48 (m, 2 H) 2.05 (d, *J*=13.30 Hz, 2 H) 1.86 (s, 1 H) 1.67 - 1.75 (m, 3 H) 1.48 - 1.61 (m, 3 H) 1.15 - 1.34 (m, 4 H) 1.05 (d, *J*=6.53 Hz, 3 H) 0.92 (t, *J*=11.04 Hz, 1 H) ; MS: MS *m/z* 872.2 (M^+-1).

Preparation of Compound 4119



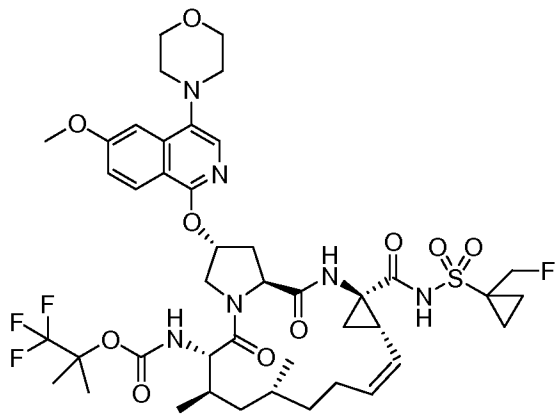
Compound 4119

Compound 4119 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4029.

Compound 4119: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-N-(1-(fluoromethyl)cyclopropylsulfonyl)-7,9-dimethyl-5,16-dioxo-6-(1-(trifluoromethyl)cyclopropanecarboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide.

^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.99 (s, 1 H) 7.92 (s, 1 H) 7.72 (d, *J*=11.54 Hz, 1 H) 7.55 - 7.61 (m, 2 H) 7.53 (s, 1 H) 5.83 (br. s., 1 H) 5.63 (d, *J*=5.27 Hz, 1 H) 5.01 (t, *J*=9.79 Hz, 1 H) 4.77 - 4.82 (m, 1 H) 4.48 - 4.65 (m, 3 H) 4.24 (dd, *J*=11.04, 8.28 Hz, 1 H) 4.00 - 4.07 (m, 7 H) 3.28 (dt, *J*=3.26, 1.63 Hz, 2 H) 2.66 - 2.75 (m, 2 H) 2.37 - 2.47 (m, 2 H) 2.03 (d, *J*=9.29 Hz, 2 H) 1.82 (s, 1 H) 1.65 - 1.76 (m, 3 H) 1.49 - 1.60 (m, 3 H) 1.19 - 1.36 (m, 4 H) 1.09 - 1.16 (m, 3 H) 1.02 (dd, *J*=18.57, 6.78 Hz, 3 H) 0.86 - 0.95 (m, 2 H) ; MS: MS *m/z* 870.4 (M^++1).

Preparation of Compound 4120

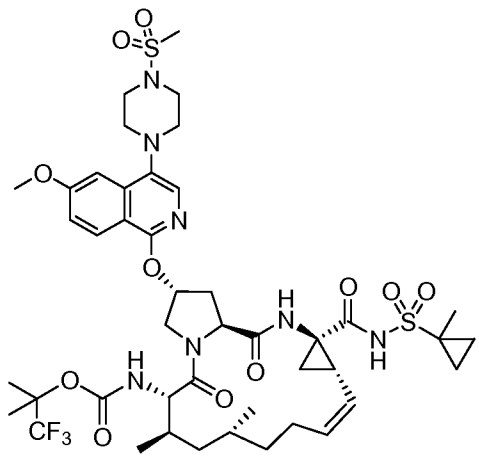


Compound 4120

Compound 4120 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4120: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(6-methoxy-4-morpholinoisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.12 (d, *J*=9.03 Hz, 1 H) 7.71 (s, 1 H) 7.46 (d, *J*=2.51 Hz, 1 H) 7.14 (dd, *J*=9.29, 2.51 Hz, 1 H) 5.84 (br. s., 1 H) 5.57 - 5.66 (m, 1 H) 5.02 (br. s., 1 H) 4.50 - 4.75 (m, 6 H) 3.94 - 4.05 (m, 8 H) 3.83 (d, *J*=10.79 Hz, 1 H) 3.28 (br. s., 1 H) 3.06 - 3.17 (m, 4 H) 2.66 - 2.77 (m, 2 H) 2.44 (ddd, *J*=13.80, 9.79, 4.27 Hz, 3 H) 1.78 - 2.03 (m, 3 H) 1.63 - 1.76 (m, 2 H) 1.57 (dd, *J*=9.41, 5.40 Hz, 1 H) 1.49 (d, *J*=7.03 Hz, 2 H) 1.14 - 1.41 (m, 6 H) 0.96 - 1.07 (m, 7 H) 0.84 (t, *J*=12.42 Hz, 1 H) ; MS: MS *m/z* 923.5 (M^+-1).

Preparation of Compound 4121

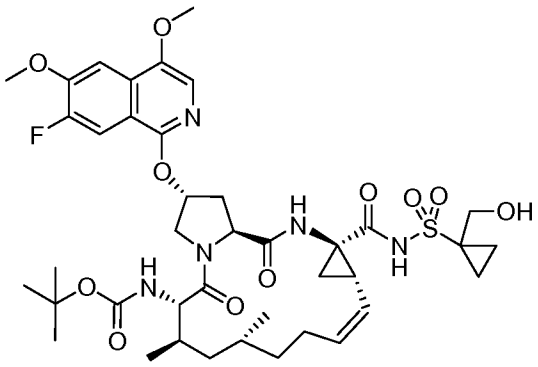


Compound 4121

Compound 4121 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4121: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(6-methoxy-4-(4-(methylsulfonyl)piperazin-1-yl)isoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.13 (d, *J*=9.03 Hz, 1 H) 7.92 (s, 1 H) 7.74 (s, 1 H) 7.43 (d, *J*=2.51 Hz, 1 H) 7.13 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.82 - 5.88 (m, 1 H) 5.58 - 5.67 (m, 1 H) 5.01 (t, *J*=10.04 Hz, 2 H) 4.72 (d, *J*=11.80 Hz, 1 H) 4.62 (d, *J*=3.01 Hz, 1 H) 4.04 (d, *J*=7.53 Hz, 1 H) 3.98 (s, 3 H) 3.87 (d, *J*=10.79 Hz, 1 H) 2.98 (s, 3 H) 2.75 (d, *J*=8.78 Hz, 3 H) 2.39 - 2.47 (m, 2 H) 1.95 - 2.05 (m, 1 H) 1.74 - 1.89 (m, 3 H) 1.63 - 1.70 (m, 1 H) 1.55 - 1.59 (m, 1 H) 1.53 (s, 3 H) 1.40 - 1.49 (m, 3 H) 1.25 - 1.32 (m, 2 H) 1.15 (s, 10 H) 0.99 - 1.04 (m, 8 H) 0.83 - 0.92 (m, 5 H). MS: MS *m/z* 931.14 (M^++1).

Preparation of Compound 4122

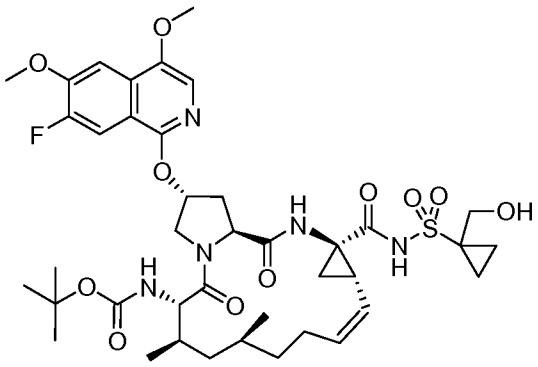


Compound 4122

Compound 4122 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4122: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-14a-(1-(hydroxymethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.72 (d, *J*=11.54 Hz, 1 H) 7.51 - 7.58 (m, 2 H) 6.66 (d, *J*=8.28 Hz, 1 H) 5.81 (br. s., 1 H) 5.61 (br. s., 1 H) 5.08 (br. s., 1 H) 4.55 - 4.71 (m, 2 H) 3.93 - 4.06 (m, 8 H) 3.78 - 3.89 (m, 2 H) 2.63 - 2.76 (m, 2 H) 2.34 - 2.49 (m, 2 H) 1.97 (br. s., 1 H) 1.76 - 1.90 (m, 2 H) 1.72 (dd, *J*=8.03, 5.52 Hz, 1 H) 1.54 - 1.63 (m, 2 H) 1.49 (d, *J*=12.30 Hz, 3 H) 1.39 (s, 1 H) 1.23 - 1.36 (m, 3 H) 1.07 - 1.21 (m, 9 H) 1.01 (dd, *J*=13.43, 6.65 Hz, 7 H) 0.82 (t, *J*=12.67 Hz, 1 H) ; MS: MS *m/z* 833.2 (M^++1).

Preparation of Compound 4123

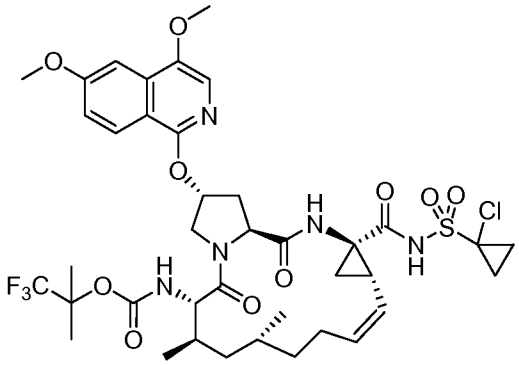


Compound 4123

Compound 4123 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4123: tert-butyl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-14a-(1-(hydroxymethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.72 (d, *J*=11.80 Hz, 1 H) 7.47 - 7.56 (m, 2 H) 5.79 (br. s., 1 H) 5.70 (d, *J*=7.28 Hz, 1 H) 5.07 (br. s., 1 H) 4.65 (d, *J*=7.28 Hz, 1 H) 4.43 (d, *J*=11.04 Hz, 1 H) 4.12 (d, *J*=6.27 Hz, 1 H) 3.95 - 4.03 (m, 7 H) 3.77 (d, *J*=12.55 Hz, 1 H) 2.64 (d, *J*=5.02 Hz, 2 H) 2.44 (br. s., 1 H) 1.92 - 2.04 (m, 2 H) 1.55 - 1.68 (m, 4 H) 1.43 (br. s., 3 H) 1.26 - 1.35 (m, 6 H) 1.22 (br. s., 9 H) 1.08 (d, *J*=6.02 Hz, 5 H) 0.90 (d, *J*=6.53 Hz, 3 H) ; MS: MS *m/z* 833.2 (M^++1).

Preparation of Compound 4124

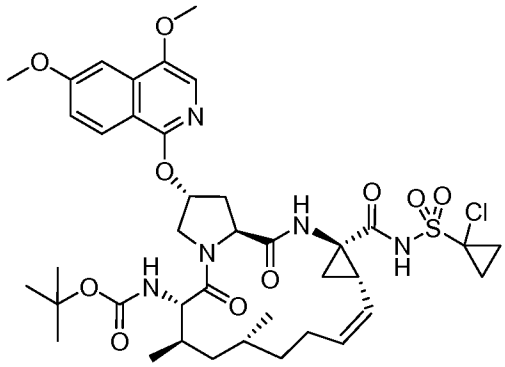


Compound 4124

Compound 4124 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4124: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-chlorocyclopropylsulfonylcarbamoyl)-2-(4,6-dimethoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.07 (d, *J*=9.03 Hz, 1 H) 7.53 (s, 1 H) 7.43 (d, *J*=2.51 Hz, 1 H) 7.14 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.80 (br. s., 1 H) 5.60 (br. s., 1 H) 4.54 - 4.74 (m, 3 H) 3.99 - 4.07 (m, 4 H) 3.95 (s, 3 H) 3.81 - 3.88 (m, 1 H) 3.28 (br. s., 1 H) 2.66 - 2.78 (m, 2 H) 2.44 (d, *J*=9.03 Hz, 2 H) 1.88 - 2.04 (m, 3 H) 1.70 - 1.87 (m, 3 H) 1.59 (d, *J*=10.29 Hz, 2 H) 1.45 (br. s., 5 H) 1.39 (s, 3 H) 1.31 (s, 1 H) 0.96 - 1.06 (m, 7 H) 0.78 - 0.87 (m, 1 H) ; MS: MS *m/z* 872.4 (M^++1).

Preparation of Compound 4125

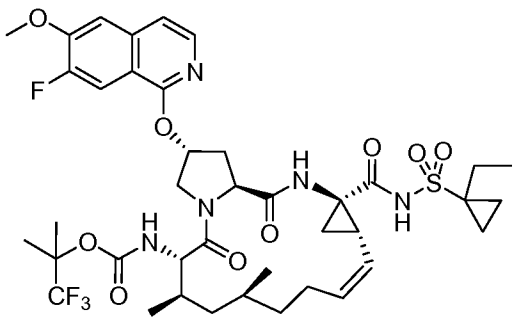


Compound 4125

Compound 4125 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4125: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-chlorocyclopropylsulfonylcarbamoyl)-2-(4,6-dimethoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.07 (d, *J*=9.29 Hz, 1 H) 7.51 (s, 1 H) 7.42 (s, 1 H) 7.12 (d, *J*=11.29 Hz, 1 H) 6.66 (d, *J*=9.03 Hz, 1 H) 5.81 (br. s., 1 H) 5.61 (s, 1 H) 5.00 (br. s., 1 H) 4.57 - 4.73 (m, 2 H) 3.99 - 4.07 (m, 4 H) 3.85 - 3.98 (m, 4 H) 3.24 - 3.29 (m, 1 H) 2.75 (d, *J*=7.28 Hz, 2 H) 2.43 (d, *J*=9.29 Hz, 2 H) 1.89 - 2.08 (m, 3 H) 1.71 - 1.88 (m, 3 H) 1.43 - 1.62 (m, 5 H) 1.23 - 1.35 (m, 3 H) 1.09 - 1.21 (m, 7 H) 1.00 (dd, *J*=10.29, 6.53 Hz, 6 H) 0.85 (d, *J*=13.30 Hz, 1 H) ; MS: MS *m/z* 818.4 (M^++1).

Preparation of Compound 4126

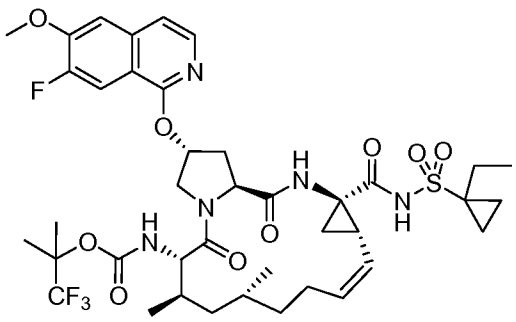


Compound 4126

Compound 4126 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4126: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(1-ethylcyclopropylsulfonylcarbamoyl)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.95 (d, *J*=5.77 Hz, 1 H) 7.79 (d, *J*=11.54 Hz, 1 H) 7.27 - 7.43 (m, 2 H) 5.90 (br. s., 1 H) 5.61 (td, *J*=10.16, 5.52 Hz, 1 H) 4.98 (t, *J*=10.16 Hz, 1 H) 4.60 - 4.75 (m, 2 H) 3.98 - 4.06 (m, 4 H) 3.82 (d, *J*=10.79 Hz, 1 H) 2.69 - 2.79 (m, 2 H) 2.44 (ddd, *J*=13.93, 10.04, 4.14 Hz, 2 H) 2.06 (dd, *J*=14.81, 7.53 Hz, 1 H) 1.87 - 2.00 (m, 2 H) 1.71 - 1.86 (m, 3 H) 1.43 - 1.67 (m, 5 H) 1.33 - 1.42 (m, 4 H) 1.18 - 1.33 (m, 2 H) 1.13 (s, 3 H) 0.88 - 1.07 (m, 9 H) 0.80 - 0.87 (m, 1 H) ; MS: MS *m/z* 855.2 (M^++1).

Preparation of Compound 4127

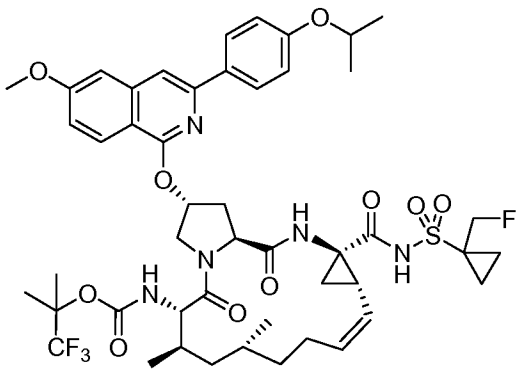


Compound 4127

Compound 4127 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4127: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-ethylcyclopropylsulfonylcarbamoyl)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.10 (s, 1 H) 7.94 (d, *J*=6.02 Hz, 1 H) 7.83 (d, *J*=11.54 Hz, 1 H) 7.39 (d, *J*=8.28 Hz, 1 H) 7.30 (d, *J*=5.77 Hz, 1 H) 5.90 (br. s., 1 H) 5.68 - 5.77 (m, 1 H) 5.02 (t, *J*=9.54 Hz, 1 H) 4.71 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.52 (d, *J*=11.80 Hz, 1 H) 4.13 (d, *J*=6.27 Hz, 1 H) 4.00 - 4.09 (m, 4 H) 2.58 - 2.77 (m, 2 H) 2.40 - 2.52 (m, 2 H) 1.91 - 2.07 (m, 3 H) 1.76 - 1.89 (m, 1 H) 1.70 (dd, *J*=8.03, 5.52 Hz, 1 H) 1.54 - 1.64 (m, 3 H) 1.36 - 1.51 (m, 6 H) 1.18 - 1.33 (m, 6 H) 1.12 (d, *J*=6.78 Hz, 3 H) 0.88 - 1.05 (m, 7 H) ; MS: MS *m/z* 855.2 (M^++1).

Preparation of Compound 4128

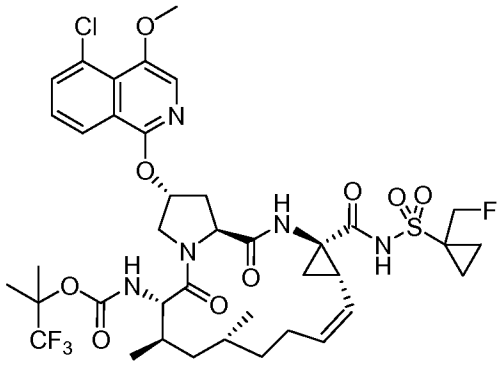


Compound 4128

Compound 4128 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4128: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.03 (s, 1 H) 8.03 - 8.14 (m, 3 H) 7.69 (s, 1 H) 7.24 (d, *J*=2.51 Hz, 1 H) 7.00 - 7.06 (m, 3 H) 6.07 (br. s., 1 H) 5.63 (td, *J*=10.29, 5.77 Hz, 1 H) 5.01 (t, *J*=9.91 Hz, 1 H) 4.60 - 4.81 (m, 4 H) 4.13 (dd, *J*=11.42, 3.64 Hz, 1 H) 3.95 (s, 3 H) 3.89 (d, *J*=10.79 Hz, 1 H) 2.67 - 2.84 (m, 2 H) 2.36 - 2.56 (m, 2 H) 1.77 - 2.05 (m, 3 H) 1.62 - 1.76 (m, 3 H) 1.44 - 1.61 (m, 4 H) 1.33 - 1.43 (m, 8 H) 1.16 - 1.31 (m, 4 H) 1.11 (s, 3 H) 1.01 (dd, *J*=18.95, 6.65 Hz, 6 H) 0.86 (t, *J*=11.80 Hz, 1 H) ; MS: MS *m/z* 975.2 (M^++1).

Preparation of Compound 4129

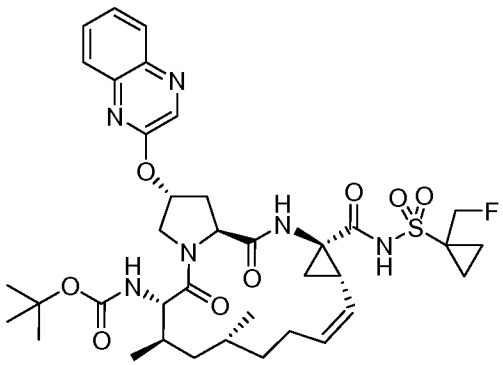


Compound 4129

Compound 4129 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4129: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(5-chloro-4-methoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.16 - 8.20 (m, 1 H) 7.76 - 7.81 (m, 1 H) 7.72 (s, 1 H) 7.48 (t, *J*=7.91 Hz, 1 H) 7.28 (d, *J*=8.03 Hz, 1 H) 5.84 (br. s., 1 H) 5.62 (d, *J*=5.52 Hz, 1 H) 5.00 (t, *J*=9.41 Hz, 1 H) 4.60 - 4.69 (m, 2 H) 3.95 - 4.04 (m, 4 H) 3.80 (dd, *J*=10.79, 7.78 Hz, 1 H) 2.61 - 2.78 (m, 3 H) 2.36 - 2.50 (m, 2 H) 2.13 - 2.22 (m, 1 H) 1.91 - 2.02 (m, 1 H) 1.76 - 1.90 (m, 2 H) 1.62 - 1.76 (m, 3 H) 1.58 (dd, *J*=9.41, 5.40 Hz, 1 H) 1.48 (br. s., 2 H) 1.30 - 1.40 (m, 3 H) 1.15 - 1.29 (m, 5 H) 0.93 - 1.05 (m, 7 H) 0.79 - 0.87 (m, 1 H) ; MS: MS *m/z* 872.4 (M^+-1).

Preparation of Compound 4130

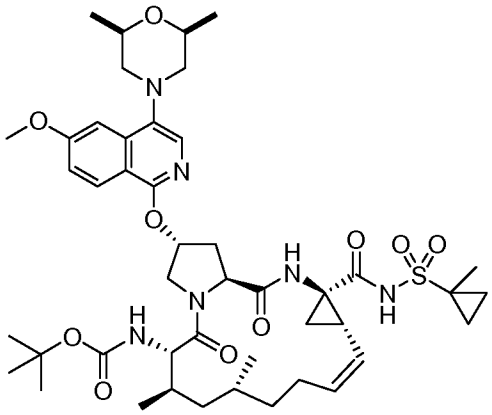


Compound 4130

Compound 4130 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4130: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-2-(quinoxalin-2-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.44 (s, 1 H) 8.00 (d, *J*=8.03 Hz, 1 H) 7.90 - 7.95 (m, 1 H) 7.77 (t, *J*=7.03 Hz, 1 H) 7.62 - 7.68 (m, 1 H) 5.92 (br. s., 1 H) 5.59 (br. s., 1 H) 4.93 - 5.04 (m, 2 H) 4.55 - 4.64 (m, 2 H) 4.05 - 4.13 (m, 1 H) 3.82 (d, *J*=10.54 Hz, 1 H) 2.66 - 2.73 (m, 2 H) 2.50 (br. s., 1 H) 2.37 (br. s., 1 H) 1.98 (br. s., 1 H) 1.82 (br. s., 2 H) 1.72 (dd, *J*=8.41, 5.40 Hz, 2 H) 1.58 (br. s., 2 H) 1.47 (br. s., 3 H) 1.25 - 1.34 (m, 5 H) 1.13 (s, 9 H) 0.93 - 1.05 (m, 7 H) 0.77 - 0.86 (m, 1 H) ; MS: MS *m/z* 757.2 (M^++1).

Preparation of Compound 4131

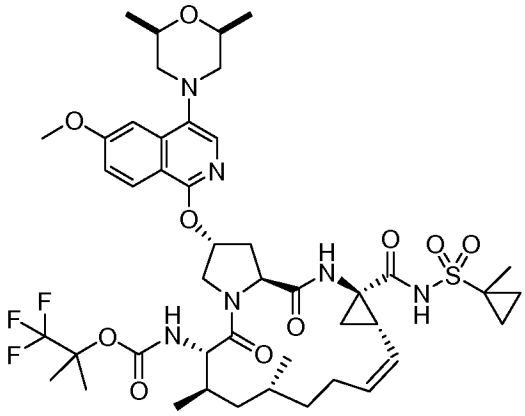


Compound 4131

Compound 4131 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4131: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-((2S,6R)-2,6-dimethylmorpholino)-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.12 (d, *J*=9.03 Hz, 1 H) 7.67 (s, 1 H) 7.42 (d, *J*=2.51 Hz, 1 H) 7.12 (dd, *J*=9.03, 2.26 Hz, 1 H) 6.63 (d, *J*=8.78 Hz, 1 H) 5.84 (br. s., 1 H) 5.58 - 5.66 (m, 1 H) 5.00 (t, *J*=9.79 Hz, 1 H) 4.68 - 4.75 (m, 1 H) 4.60 (dd, *J*=16.31, 9.03 Hz, 1 H) 3.98 - 4.06 (m, 3 H) 3.82 - 3.97 (m, 4 H) 3.16 (d, *J*=11.29 Hz, 3 H) 2.68 - 2.78 (m, 2 H) 2.50 - 2.65 (m, 2 H) 2.37 - 2.48 (m, 2 H) 1.92 - 2.03 (m, 1 H) 1.73 - 1.90 (m, 3 H) 1.66 (d, *J*=10.04 Hz, 1 H) 1.49 - 1.59 (m, 5 H) 1.38 - 1.48 (m, 3 H) 1.28 - 1.37 (m, 3 H) 1.19 - 1.28 (m, 5 H) 1.14 (s, 7 H) 1.00 (dd, *J*=9.79, 6.78 Hz, 5 H) 0.79 - 0.93 (m, 2 H) ; MS: MS *m/z* 882.6 (M^++1).

Preparation of Compound 4132

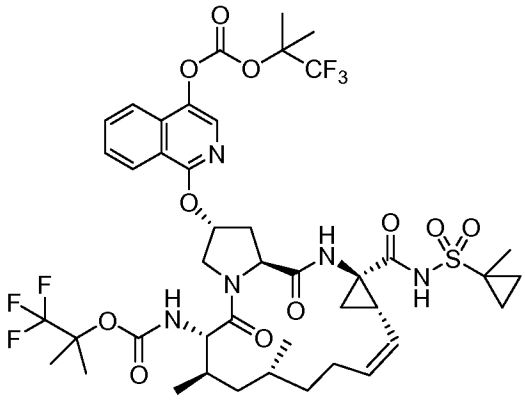


Compound 4132

Compound 4132 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4132: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-((2S,6R)-2,6-dimethylmorpholino)-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.08 (s, 1 H) 8.13 (d, *J*=9.29 Hz, 1 H) 7.65 - 7.70 (m, 1 H) 7.44 (d, *J*=2.51 Hz, 1 H) 7.15 (dd, *J*=9.29, 2.51 Hz, 1 H) 5.84 (br. s., 1 H) 5.62 (dt, *J*=10.29, 5.14 Hz, 1 H) 4.97 - 5.06 (m, 2 H) 4.61 - 4.77 (m, 2 H) 3.99 - 4.07 (m, 3 H) 3.93 - 3.99 (m, 3 H) 3.82 (d, *J*=10.79 Hz, 1 H) 3.12 - 3.22 (m, 2 H) 2.70 - 2.79 (m, 2 H) 2.53 - 2.66 (m, 2 H) 2.44 (ddd, *J*=13.68, 9.91, 4.27 Hz, 2 H) 1.86 - 2.03 (m, 2 H) 1.73 - 1.84 (m, 2 H) 1.63 - 1.73 (m, 1 H) 1.57 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.41 - 1.54 (m, 5 H) 1.30 - 1.39 (m, 4 H) 1.17 - 1.29 (m, 7 H) 0.96 - 1.09 (m, 9 H) 0.79 - 0.94 (m, 2 H) ; MS: MS *m/z* 935.8 (M^++1).

Preparation of Compound 4133

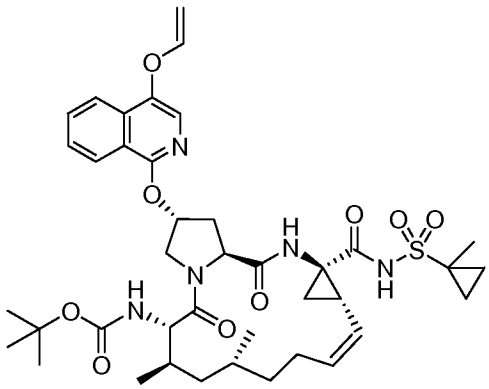


Compound 4133

Compound 4133 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4133: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(4-((1,1,1-trifluoro-2-methylpropan-2-yloxy)carbonyloxy)isoquinolin-1-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.27 (d, *J*=8.53 Hz, 1 H) 7.99 (s, 1 H) 7.79 - 7.87 (m, 2 H) 7.64 (t, *J*=7.53 Hz, 1 H) 5.93 (br. s., 1 H) 5.62 (d, *J*=4.52 Hz, 1 H) 5.05 (br. s., 1 H) 4.68 (dd, *J*=10.16, 7.15 Hz, 1 H) 4.04 (dd, *J*=11.54, 3.01 Hz, 1 H) 3.82 (d, *J*=10.79 Hz, 1 H) 2.79 (dd, *J*=13.30, 7.28 Hz, 1 H) 2.40 - 2.52 (m, 2 H) 1.94 - 2.03 (m, 2 H) 1.79 - 1.85 (m, 7 H) 1.74 - 1.78 (m, 1 H) 1.57 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.52 (s, 3 H) 1.39 - 1.46 (m, 2 H) 1.29 - 1.35 (m, 5 H) 1.22 - 1.28 (m, 2 H) 1.00 (dd, *J*=10.16, 6.65 Hz, 6 H) 0.91 (s, 5 H) 0.80 - 0.89 (m, 3 H) ; MS: MS *m/z* 962.6 (M^++1).

Preparation of Compound 4134

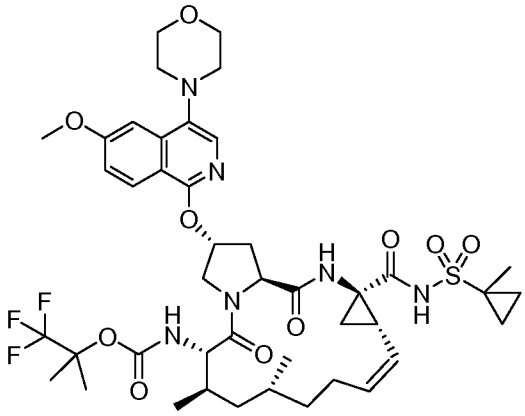


Compound 4134

Compound 4134 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4134: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(4-(vinyloxy)isoquinolin-1-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.22 (d, *J*=8.28 Hz, 1 H) 8.03 (d, *J*=8.53 Hz, 1 H) 7.77 (t, *J*=7.53 Hz, 1 H) 7.72 (s, 1 H) 7.56 - 7.62 (m, 1 H) 6.86 (dd, *J*=13.68, 6.15 Hz, 1 H) 6.63 (d, *J*=8.53 Hz, 1 H) 5.89 (br. s., 1 H) 5.63 (td, *J*=10.29, 5.52 Hz, 1 H) 5.01 (t, *J*=10.04 Hz, 1 H) 4.71 - 4.80 (m, 2 H) 4.64 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.48 (dd, *J*=6.02, 1.51 Hz, 1 H) 4.05 (dd, *J*=11.42, 3.39 Hz, 1 H) 3.84 - 3.91 (m, 1 H) 2.70 - 2.81 (m, 2 H) 2.38 - 2.50 (m, 2 H) 1.98 (t, *J*=12.92 Hz, 1 H) 1.73 - 1.91 (m, 3 H) 1.62 - 1.70 (m, 1 H) 1.57 (dd, *J*=9.41, 5.65 Hz, 1 H) 1.39 - 1.54 (m, 6 H) 1.18 - 1.36 (m, 3 H) 1.11 (s, 9 H) 1.00 (dd, *J*=10.67, 6.65 Hz, 4 H) 0.79 - 0.94 (m, 3 H) ; MS: MS *m/z* 780.4 (M^++1).

Preparation of Compound 4135

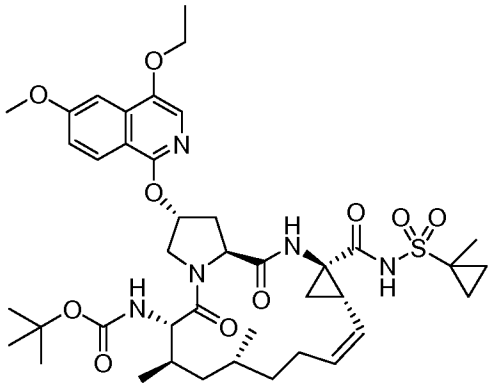


Compound 4135

Compound 4135 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4135: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(6-methoxy-4-morpholinoisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.06 (s, 1 H) 8.13 (d, *J*=9.03 Hz, 1 H) 7.71 (s, 1 H) 7.47 (d, *J*=2.26 Hz, 1 H) 7.15 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.85 (br. s., 1 H) 5.60 - 5.68 (m, 1 H) 5.01 (t, *J*=10.04 Hz, 1 H) 4.74 (d, *J*=11.54 Hz, 1 H) 4.65 (dd, *J*=10.29, 7.03 Hz, 1 H) 4.03 (dd, *J*=11.42, 3.39 Hz, 1 H) 3.93 - 3.99 (m, 7 H) 3.83 (d, *J*=10.79 Hz, 1 H) 3.29 (dd, *J*=3.26, 1.51 Hz, 1 H) 3.06 - 3.13 (m, 4 H) 2.69 - 2.79 (m, 2 H) 2.44 (ddd, *J*=13.87, 9.98, 4.27 Hz, 2 H) 1.86 - 2.04 (m, 2 H) 1.75 - 1.85 (m, 2 H) 1.63 - 1.70 (m, 1 H) 1.55 - 1.61 (m, 1 H) 1.40 - 1.55 (m, 6 H) 1.30 - 1.37 (m, 4 H) 1.24 (d, *J*=13.55 Hz, 1 H) 0.96 - 1.05 (m, 7 H) 0.80 - 0.92 (m, 3 H) ; MS: MS *m/z* 905.4 (M^+-1).

Preparation of Compound 4136

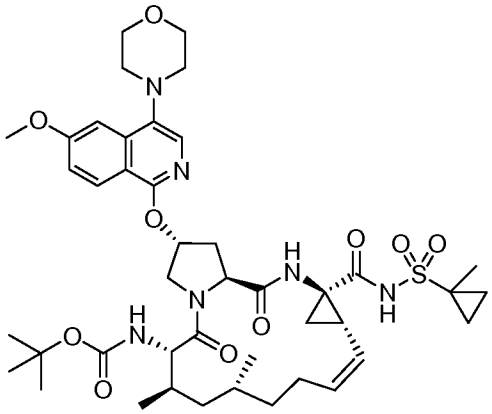


Compound 4136

Compound 4136 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4136: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxy-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.07 (d, *J*=9.03 Hz, 1 H) 7.50 (s, 1 H) 7.43 (d, *J*=2.26 Hz, 1 H) 7.12 (dd, *J*=9.16, 2.38 Hz, 1 H) 6.62 (d, *J*=8.53 Hz, 1 H) 5.81 (br. s., 1 H) 5.62 (dt, *J*=10.04, 5.02 Hz, 1 H) 5.00 (t, *J*=10.04 Hz, 1 H) 4.68 (d, *J*=11.29 Hz, 1 H) 4.60 (dd, *J*=9.79, 7.53 Hz, 1 H) 4.23 (q, *J*=7.03 Hz, 2 H) 4.03 (dd, *J*=11.42, 3.39 Hz, 1 H) 3.95 (s, 3 H) 3.85 - 3.92 (m, 1 H) 2.68 - 2.80 (m, 2 H) 2.36 - 2.49 (m, 2 H) 1.98 (br. s., 1 H) 1.84 (dd, *J*=14.93, 5.65 Hz, 2 H) 1.73 - 1.80 (m, 2 H) 1.62 - 1.69 (m, 1 H) 1.50 - 1.59 (m, 7 H) 1.40 - 1.48 (m, 2 H) 1.23 - 1.33 (m, 3 H) 1.17 (s, 7 H) 0.97 - 1.04 (m, 5 H) 0.86 - 0.93 (m, 3 H) 0.79 - 0.85 (m, 1 H) ; MS: MS *m/z* 812.4 (M^++1).

Preparation of Compound 4137

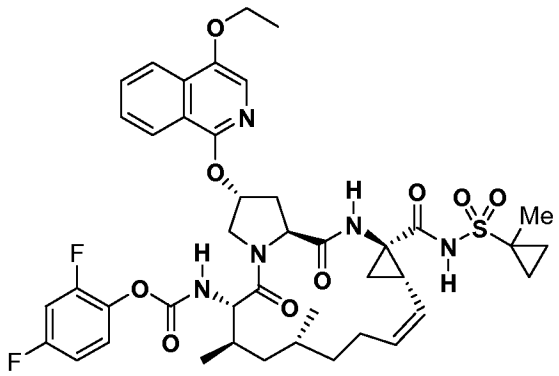


Compound 4137

Compound 4137 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4137: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(6-methoxy-4-morpholinoisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.12 (d, *J*=9.29 Hz, 1 H) 7.70 (s, 1 H) 7.45 (d, *J*=2.51 Hz, 1 H) 7.12 (dd, *J*=9.03, 2.26 Hz, 1 H) 6.63 (d, *J*=8.28 Hz, 1 H) 5.84 (br. s., 1 H) 5.62 (td, *J*=10.16, 5.77 Hz, 1 H) 5.00 (t, *J*=10.04 Hz, 1 H) 4.69 - 4.76 (m, 1 H) 4.61 (dd, *J*=9.79, 7.28 Hz, 1 H) 4.04 (dd, *J*=11.42, 3.14 Hz, 1 H) 3.93 - 3.99 (m, 7 H) 3.84 - 3.91 (m, 1 H) 3.35 (br. s., 2 H) 3.06 - 3.12 (m, 4 H) 2.68 - 2.79 (m, 2 H) 2.38 - 2.51 (m, 2 H) 1.93 - 2.07 (m, 1 H) 1.74 - 1.91 (m, 3 H) 1.62 - 1.72 (m, 1 H) 1.56 (dd, *J*=9.41, 5.65 Hz, 1 H) 1.46 - 1.53 (m, 2 H) 1.39 - 1.45 (m, 2 H) 1.21 - 1.38 (m, 2 H) 1.14 (s, 9 H) 1.00 (dd, *J*=9.91, 6.65 Hz, 4 H) 0.86 - 0.95 (m, 3 H) 0.80 - 0.86 (m, 1 H) ; MS: MS *m/z* 853.4 (M^++1).

Preparation of Compound 4138

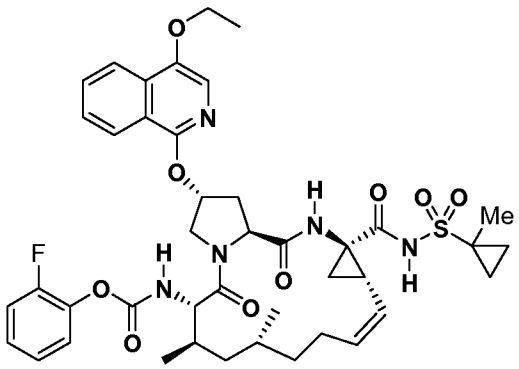


Compound 4138

Compound 4138 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4138: 2,4-difluorophenyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.12 (t, *J*=9.29 Hz, 2 H) 7.74 (t, *J*=7.65 Hz, 2 H) 7.46 - 7.54 (m, 2 H) 6.76 - 6.95 (m, 2 H) 5.81 (br. s., 1 H) 5.59 - 5.72 (m, 1 H) 5.04 (br. s., 1 H) 4.50 - 4.70 (m, 2 H) 3.96 - 4.24 (m, 4 H) 3.25 - 3.31 (m, 2 H) 2.67 - 2.82 (m, 2 H) 2.36 - 2.57 (m, 2 H) 1.91 - 2.12 (m, 2 H) 1.73 - 1.88 (m, 2 H) 1.62 - 1.73 (m, 1 H) 1.53 (s, 8 H) 1.20 - 1.37 (m, 1 H) 1.01 - 1.17 (m, 6 H) 0.82 - 0.96 (m, 3 H) ; MS: MS *m/z* 838.2 (M^++1).

Preparation of Compound 4139

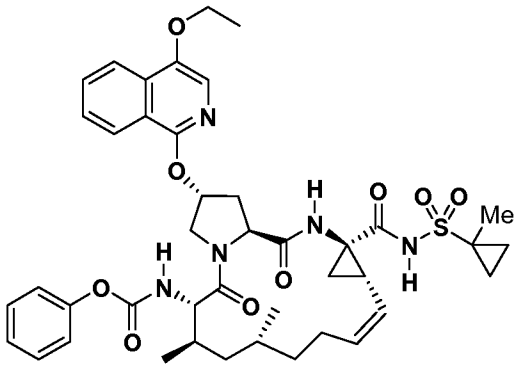


Compound 4139

Compound 4139 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4139: 2-fluorophenyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.09 - 8.15 (m, 2 H) 7.42 - 7.51 (m, 2 H) 7.17 - 7.27 (m, 2 H) 7.03 - 7.11 (m, 2 H) 6.86 (td, *J*=8.03, 1.51 Hz, 1 H) 5.83 (br. s., 1 H) 5.59 - 5.70 (m, 1 H) 4.98 - 5.08 (m, 1 H) 4.85 (s, 1 H) 4.60 - 4.66 (m, 2 H) 4.01 - 4.23 (m, 5 H) 3.28 (br. s., 1 H) 2.72 - 2.84 (m, 2 H) 2.39 - 2.55 (m, 2 H) 2.03 (dd, *J*=11.80, 5.77 Hz, 2 H) 1.82 - 1.91 (m, 1 H) 1.77 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.64 - 1.70 (m, 1 H) 1.50 - 1.61 (m, 9 H) 1.41 - 1.46 (m, 1 H) 1.25 - 1.32 (m, 2 H) 1.10 (d, *J*=6.53 Hz, 2 H) 1.05 (d, *J*=6.78 Hz, 2 H) 0.87 - 0.95 (m, 2 H); MS: MS *m/z* 820.4 (M^++1).

Preparation of Compound 4140

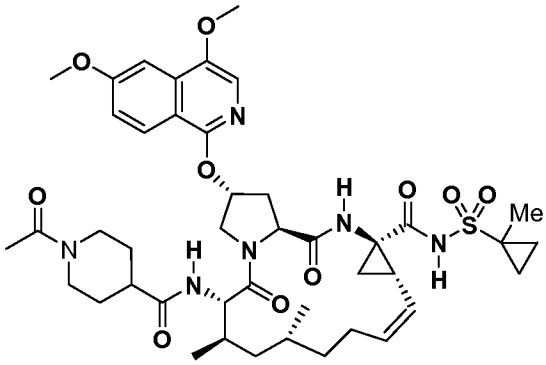


Compound 4140

Compound 440 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4140: phenyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.10 - 8.16 (m, 2 H) 7.68 - 7.79 (m, 2 H) 7.50 (s, 1 H) 7.39 - 7.46 (m, 1 H) 7.12 - 7.27 (m, 3 H) 6.73 - 6.79 (m, 2 H) 5.84 (br. s., 1 H) 5.64 (td, *J*=10.04, 5.77 Hz, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.60 - 4.68 (m, 2 H) 4.14 - 4.24 (m, 2 H) 4.00 - 4.11 (m, 2 H) 2.72 - 2.82 (m, 2 H) 2.39 - 2.53 (m, 2 H) 1.96 - 2.08 (m, 2 H) 1.75 - 1.90 (m, 2 H) 1.63 - 1.71 (m, 1 H) 1.48 - 1.60 (m, 9 H) 1.40 - 1.47 (m, 1 H) 1.22 - 1.35 (m, 2 H) 1.06 (dd, *J*=19.32, 6.78 Hz, 5 H) 0.84 - 0.94 (m, 3 H) ; MS: MS *m/z* 802.5 (M^++1).

Preparation of Compound 4141

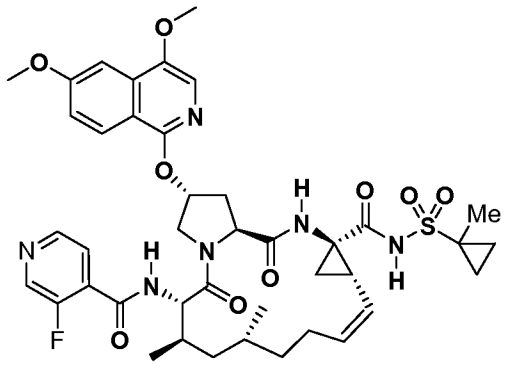


Compound 4141

Compound 4141 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4029.

Compound 4141: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(1-acetylpiperidine-4-carboxamido)-2-(4,6-dimethoxyisoquinolin-1-yloxy)-7,9-dimethyl-N-(1-methylcyclopropylsulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.04 (s, 1 H) 7.96 - 8.07 (m, 2 H) 7.52 (d, *J*=7.78 Hz, 1 H) 7.45 (d, *J*=2.51 Hz, 1 H) 7.17 (ddd, *J*=11.73, 9.10, 2.51 Hz, 1 H) 5.83 (d, *J*=2.76 Hz, 1 H) 5.64 (td, *J*=10.04, 5.77 Hz, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.55 - 4.66 (m, 2 H) 4.18 - 4.32 (m, 2 H) 3.94 - 4.08 (m, 7 H) 3.75 (d, *J*=13.55 Hz, 1 H) 3.02 (t, *J*=11.17 Hz, 1 H) 2.86 - 2.95 (m, 1 H) 2.68 - 2.82 (m, 2 H) 2.49 - 2.66 (m, 1 H) 2.36 - 2.47 (m, 2 H) 2.28 (br. s., 1 H) 1.94 - 2.10 (m, 5 H) 1.75 - 1.84 (m, 2 H) 1.63 - 1.71 (m, 1 H) 1.46 - 1.62 (m, 7 H) 1.31 - 1.45 (m, 2 H) 1.11 - 1.29 (m, 2 H) 0.92 - 1.07 (m, 7 H) 0.79 - 0.91 (m, 2 H) ; MS: MS *m/z* 849.2 (M^+-1).

Preparation of Compound 4142

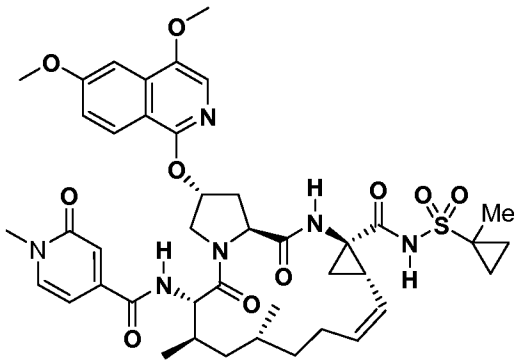


Compound 4142

Compound 4142 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4029.

Compound 4142: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4,6-dimethoxyisoquinolin-1-yloxy)-6-(3-fluoroisonicotinamido)-7,9-dimethyl-N-(1-methylcyclopropylsulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.07 (s, 1 H) 8.50 (d, *J*=1.76 Hz, 1 H) 8.34 (d, *J*=4.52 Hz, 1 H) 8.08 (d, *J*=9.29 Hz, 1 H) 7.50 (s, 1 H) 7.39 (d, *J*=2.51 Hz, 1 H) 7.16 (dd, *J*=9.29, 2.01 Hz, 1 H) 7.05 (t, *J*=5.52 Hz, 1 H) 5.87 (br. s., 1 H) 5.64 (td, *J*=10.16, 6.27 Hz, 1 H) 5.03 (t, *J*=9.91 Hz, 1 H) 4.73 - 4.82 (m, 2 H) 4.68 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.35 - 4.42 (m, 1 H) 4.11 (dd, *J*=11.67, 3.39 Hz, 1 H) 4.04 (s, 4 H) 3.95 (s, 4 H) 3.29 (dd, *J*=3.26, 1.51 Hz, 1 H) 2.72 - 2.85 (m, 3 H) 2.48 (ddd, *J*=13.93, 10.04, 3.89 Hz, 3 H) 1.97 - 2.16 (m, 2 H) 1.86 (dd, *J*=13.18, 5.90 Hz, 1 H) 1.78 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.63 - 1.72 (m, 1 H) 1.50 - 1.62 (m, 3 H) 1.23 - 1.49 (m, 3 H) 1.00 - 1.08 (m, 3 H) 0.86 - 0.96 (m, 2 H) ; MS: MS *m/z* 821.4 (M^++1).

Preparation of Compound 4143

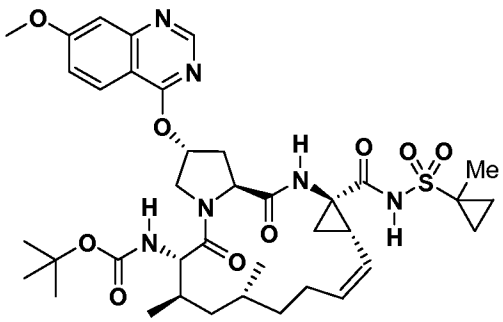


Compound 4143

Compound 4143 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4029.

Compound 4143: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4,6-dimethoxyisoquinolin-1-yloxy)-7,9-dimethyl-6-(1-methyl-2-oxo-1,2-dihydropyridine-4-carboxamido)-N-(1-methylcyclopropylsulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.06 (s, 1 H) 8.65 (d, *J*=8.28 Hz, 1 H) 8.02 (d, *J*=9.29 Hz, 1 H) 7.59 (d, *J*=6.78 Hz, 1 H) 7.49 (s, 1 H) 7.42 (d, *J*=2.51 Hz, 1 H) 7.12 (dd, *J*=9.03, 2.51 Hz, 1 H) 6.61 (d, *J*=1.51 Hz, 1 H) 6.25 (dd, *J*=6.90, 1.88 Hz, 1 H) 5.85 (br. s., 1 H) 5.63 (td, *J*=9.91, 6.27 Hz, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.76 (d, *J*=11.29 Hz, 1 H) 4.64 (dd, *J*=9.79, 7.28 Hz, 1 H) 4.29 - 4.36 (m, 1 H) 4.02 - 4.09 (m, 4 H) 3.96 (s, 3 H) 3.57 (s, 3 H) 2.71 - 2.81 (m, 2 H) 2.46 (ddd, *J*=13.87, 9.98, 4.02 Hz, 2 H) 1.97 - 2.18 (m, 2 H) 1.75 - 1.88 (m, 2 H) 1.63 - 1.72 (m, 1 H) 1.49 - 1.60 (m, 6 H) 1.21 - 1.47 (m, 3 H) 1.01 (dd, *J*=14.43, 6.65 Hz, 4 H) 0.84 - 0.94 (m, 3 H) ; MS: MS *m/z* 833.5 (M^++1).

Preparation of Compound 4144

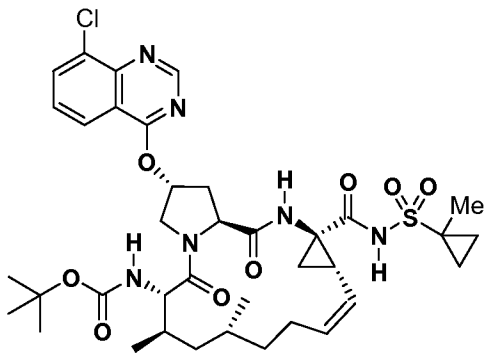


Compound 4144

Compound 4144 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4144: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-methoxyquinazolin-4-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.73 (s, 1 H) 8.09 (d, *J*=9.03 Hz, 1 H) 7.17 - 7.28 (m, 2 H) 6.00 (br. s., 1 H) 5.63 (td, *J*=10.23, 5.90 Hz, 1 H) 5.01 (t, *J*=10.16 Hz, 1 H) 4.65 (dd, *J*=9.91, 7.15 Hz, 1 H) 4.06 (dd, *J*=11.92, 3.39 Hz, 1 H) 3.98 (s, 3 H) 3.81 (d, *J*=10.79 Hz, 1 H) 2.70 - 2.86 (m, 3 H) 2.38 - 2.53 (m, 2 H) 1.98 (br. s., 1 H) 1.75 - 1.87 (m, 3 H) 1.55 - 1.70 (m, 2 H) 1.40 - 1.54 (m, 6 H) 1.19 - 1.35 (m, 3 H) 1.08 (s, 7 H) 1.00 (dd, *J*=9.41, 6.65 Hz, 6 H) 0.80 - 0.95 (m, 3 H) ; MS: MS *m/z* 769.4 (M^++1).

Preparation of Compound 4145

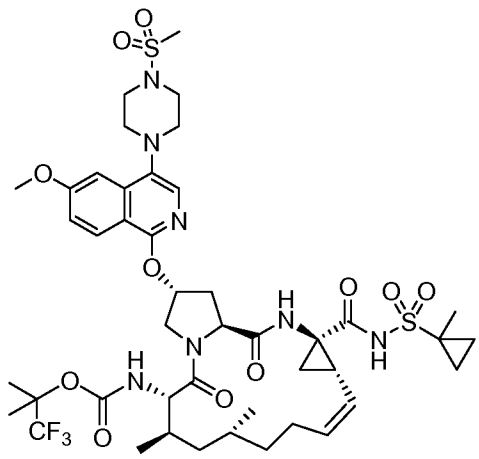


Compound 4145

Compound 4145 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4145: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(8-chloroquinazolin-4-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.89 (s, 1 H) 8.17 (dd, *J*=8.28, 1.25 Hz, 1 H) 8.05 (dd, *J*=7.65, 1.13 Hz, 1 H) 7.58 (t, *J*=7.91 Hz, 1 H) 6.64 (d, *J*=7.78 Hz, 1 H) 6.01 (br. s., 1 H) 5.59 - 5.67 (m, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.93 (d, *J*=10.54 Hz, 1 H) 4.67 (dd, *J*=10.16, 7.15 Hz, 1 H) 4.06 (dd, *J*=12.05, 3.01 Hz, 1 H) 3.77 (dd, *J*=10.42, 8.16 Hz, 1 H) 3.27 (dt, *J*=3.33, 1.73 Hz, 1 H) 2.82 (dd, *J*=14.56, 6.78 Hz, 1 H) 2.68 - 2.77 (m, 1 H) 2.36 - 2.57 (m, 2 H) 1.91 - 2.03 (m, 1 H) 1.74 - 1.85 (m, 3 H) 1.67 (d, *J*=11.04 Hz, 1 H) 1.58 (dd, *J*=9.29, 5.52 Hz, 1 H) 1.40 - 1.54 (m, 6 H) 1.31 (s, 3 H) 1.09 - 1.27 (m, 2 H) 0.96 - 1.05 (m, 10 H) 0.89 (t, *J*=9.54 Hz, 3 H) 0.79 - 0.85 (m, 1 H) ; MS: MS *m/z* 773.3 (M^++1).

Preparation of Compound 4146

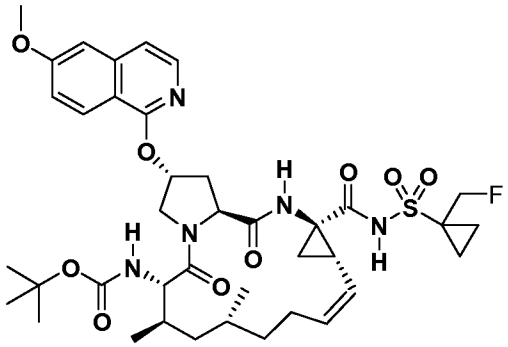


Compound 4146

Compound 4146 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4146: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(6-methoxy-4-(4-(methylsulfonyl)piperazin-1-yl)isoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.05 (s, 1 H) 8.13 (d, *J*=9.04 Hz, 1 H) 7.75 (s, 1 H) 7.44 (d, *J*=2.26 Hz, 1 H) 7.15 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.85 (br. s., 1 H) 5.63 (td, *J*=9.91, 5.77 Hz, 1 H) 5.01 (t, *J*=10.04 Hz, 2 H) 4.73 (d, *J*=11.29 Hz, 1 H) 4.65 (dd, *J*=10.16, 7.15 Hz, 1 H) 3.96 - 4.05 (m, 6 H) 3.83 (d, *J*=10.79 Hz, 1 H) 2.98 (s, 3 H) 2.67 - 2.78 (m, 2 H) 2.38 - 2.52 (m, 2 H) 1.75 - 2.04 (m, 4 H) 1.64 - 1.71 (m, 1 H) 1.41 - 1.60 (m, 8 H) 1.37 (s, 5 H) 1.20 - 1.31 (m, 3 H) 0.98 - 1.04 (m, 8 H) 0.82 - 0.94 (m, 5 H). MS: MS *m/z* 985.11 (M^++1).

Preparation of Compound 4147

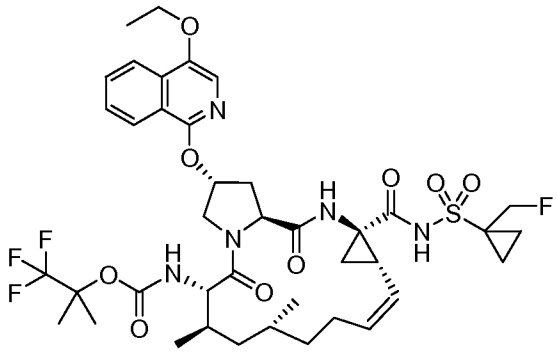


Compound 4147

Compound 4147 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4147: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.12 (d, *J*=9.03 Hz, 1 H) 7.90 - 7.94 (m, 1 H) 7.26 (d, *J*=5.77 Hz, 1 H) 7.20 (d, *J*=2.51 Hz, 1 H) 7.10 (dd, *J*=9.29, 2.51 Hz, 1 H) 6.64 (d, *J*=8.28 Hz, 1 H) 5.89 (br. s., 1 H) 5.62 (d, *J*=5.77 Hz, 1 H) 4.96 - 5.05 (m, 1 H) 4.79 (d, *J*=12.80 Hz, 1 H) 4.71 (d, *J*=11.29 Hz, 1 H) 4.48 - 4.67 (m, 2 H) 4.06 (dd, *J*=11.67, 3.39 Hz, 1 H) 3.86 - 3.98 (m, 5 H) 3.29 (d, *J*=1.76 Hz, 1 H) 2.68 - 2.77 (m, 2 H) 2.39 - 2.50 (m, 2 H) 1.97 (br. s., 1 H) 1.78 - 1.91 (m, 2 H) 1.72 (dd, *J*=8.53, 5.52 Hz, 3 H) 1.57 (dd, *J*=9.41, 5.65 Hz, 1 H) 1.43 - 1.53 (m, 2 H) 1.23 - 1.33 (m, 3 H) 1.18 (s, 5 H) 1.13 (br. s., 1 H) 1.02 (dd, *J*=12.05, 6.78 Hz, 7 H) 0.85 (t, *J*=11.80 Hz, 1 H) ; MS: MS *m/z* 786.5 (M^++1).

Preparation of Compound 4149

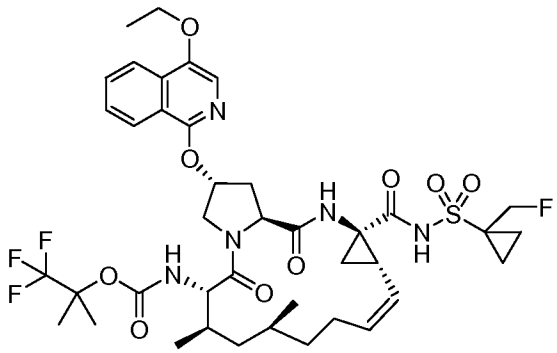


Compound 4149

Compound 4149 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4149: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17 (dd, *J*=16.56, 8.28 Hz, 2 H) 7.75 (td, *J*=7.65, 1.25 Hz, 1 H) 7.55 - 7.61 (m, 2 H) 5.84 (br. s., 1 H) 5.71 (d, *J*=10.04 Hz, 1 H) 5.07 (br. s., 1 H) 4.60 - 4.83 (m, 2 H) 4.49 - 4.59 (m, 1 H) 4.24 (q, *J*=6.94 Hz, 2 H) 4.01 - 4.15 (m, 2 H) 2.67 - 2.78 (m, 1 H) 2.61 (br. s., 1 H) 2.47 (ddd, *J*=13.80, 9.66, 4.14 Hz, 2 H) 1.92 - 2.07 (m, 2 H) 1.59 - 1.74 (m, 5 H) 1.55 (t, *J*=7.03 Hz, 4 H) 1.35 - 1.50 (m, 5 H) 1.21 - 1.33 (m, 3 H) 1.13 - 1.20 (m, 4 H) 1.10 (d, *J*=6.78 Hz, 3 H) 0.97 - 1.05 (m, 1 H) 0.94 (d, *J*=7.03 Hz, 3 H) ; MS: MS *m/z* 854.4 (M^++1).

Preparation of Compound 4150

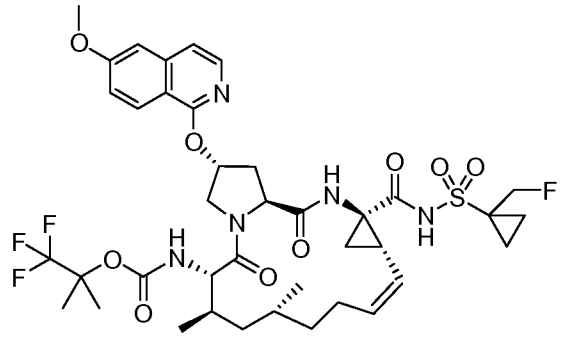


Compound 4150

Compound 4150 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4150: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-(4-ethoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.15 (t, *J*=7.28 Hz, 2 H) 7.74 (ddd, *J*=8.28, 7.15, 0.88 Hz, 1 H) 7.52 - 7.60 (m, 2 H) 5.80 - 5.85 (m, 1 H) 5.61 (td, *J*=10.23, 5.90 Hz, 1 H) 5.03 (br. s., 1 H) 4.78 (t, *J*=12.17 Hz, 2 H) 4.60 - 4.69 (m, 2 H) 4.52 (d, *J*=11.29 Hz, 1 H) 4.24 (q, *J*=6.86 Hz, 2 H) 4.02 (dd, *J*=11.54, 3.26 Hz, 1 H) 3.83 (d, *J*=10.79 Hz, 1 H) 2.65 - 2.79 (m, 2 H) 2.37 - 2.50 (m, 2 H) 1.77 - 2.03 (m, 3 H) 1.62 - 1.75 (m, 3 H) 1.41 - 1.61 (m, 7 H) 1.14 - 1.40 (m, 7 H) 0.94 - 1.07 (m, 7 H) 0.83 (t, *J*=11.80 Hz, 1 H) ; MS: MS *m/z* 854.4 (M^++1).

Preparation of Compound 4151

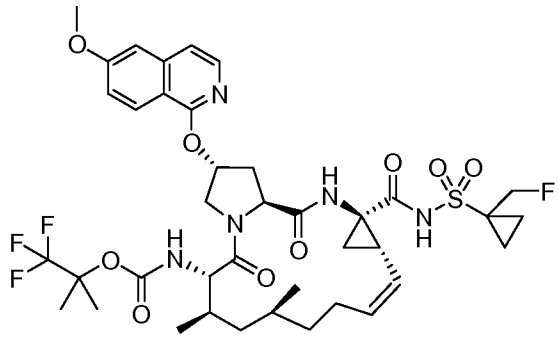


Compound 4151

Compound 4151 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4151: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.10 (d, *J*=9.03 Hz, 1 H) 7.93 (d, *J*=6.02 Hz, 1 H) 7.26 - 7.35 (m, 2 H) 7.22 (d, *J*=2.26 Hz, 1 H) 7.11 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.88 (t, *J*=3.26 Hz, 1 H) 5.62 (d, *J*=5.52 Hz, 1 H) 5.00 (t, *J*=10.04 Hz, 1 H) 4.72 - 4.83 (m, 2 H) 4.61 - 4.68 (m, 2 H) 4.51 (d, *J*=11.04 Hz, 1 H) 4.03 (dd, *J*=11.54, 3.51 Hz, 1 H) 3.95 (s, 3 H) 3.84 (dd, *J*=10.67, 8.16 Hz, 1 H) 2.66 - 2.78 (m, 2 H) 2.35 - 2.51 (m, 2 H) 1.76 - 2.02 (m, 3 H) 1.63 - 1.75 (m, 3 H) 1.58 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.43 - 1.53 (m, 2 H) 1.38 (s, 3 H) 1.15 - 1.34 (m, 4 H) 0.95 - 1.08 (m, 9 H) 0.81 - 0.88 (m, 1 H) ; MS: MS *m/z* 839.4 (M^+-1).

Preparation of Compound 4152

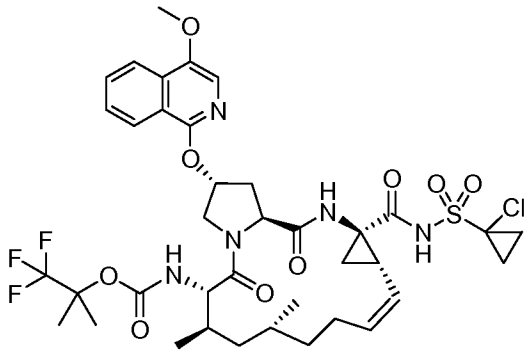


Compound 4152

Compound 4152 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4152: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.13 (d, *J*=9.03 Hz, 1 H) 7.93 (d, *J*=5.77 Hz, 1 H) 7.20 - 7.30 (m, 3 H) 7.12 (dd, *J*=9.29, 2.51 Hz, 1 H) 5.89 (br. s., 1 H) 5.69 - 5.77 (m, 1 H) 5.04 (t, *J*=9.54 Hz, 1 H) 4.92 - 4.98 (m, 1 H) 4.76 - 4.85 (m, 1 H) 4.60 - 4.75 (m, 2 H) 4.47 - 4.59 (m, 2 H) 4.03 - 4.17 (m, 2 H) 3.95 (s, 3 H) 2.57 - 2.76 (m, 2 H) 2.42 - 2.52 (m, 2 H) 1.90 - 2.07 (m, 2 H) 1.54 - 1.74 (m, 4 H) 1.38 - 1.51 (m, 5 H) 1.15 - 1.37 (m, 7 H) 1.11 (d, *J*=6.78 Hz, 4 H) 0.88 - 0.97 (m, 1 H) ; MS: MS *m/z* 839.4 (M^+-1).

Preparation of Compound 4153

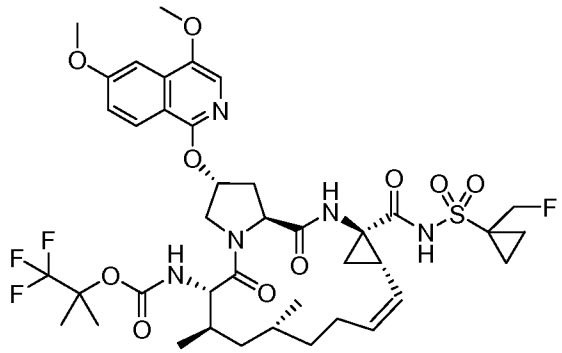


Compound 4153

Compound 44153 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4153: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-chlorocyclopropylsulfonylcarbamoyl)-2-(4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.15 (dd, *J*=17.57, 8.28 Hz, 2 H) 7.74 (td, *J*=7.65, 1.25 Hz, 1 H) 7.55 - 7.60 (m, 2 H) 5.84 (br. s., 1 H) 5.62 (d, *J*=5.77 Hz, 1 H) 4.94 - 5.08 (m, 1 H) 4.73 - 4.81 (m, 1 H) 4.67 (dd, *J*=10.29, 7.03 Hz, 1 H) 3.99 - 4.07 (m, 4 H) 3.80 - 3.88 (m, 1 H) 3.29 (d, *J*=1.76 Hz, 1 H) 2.75 (dd, *J*=13.93, 6.90 Hz, 2 H) 2.45 (ddd, *J*=13.87, 9.98, 4.27 Hz, 2 H) 1.85 - 2.08 (m, 4 H) 1.72 - 1.85 (m, 3 H) 1.60 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.41 - 1.54 (m, 3 H) 1.22 - 1.40 (m, 5 H) 1.06 - 1.20 (m, 1 H) 0.94 - 1.04 (m, 7 H) 0.79 - 0.93 (m, 1 H) ; MS: MS *m/z* 842.7 (M^++1).

Preparation of Compound 4154

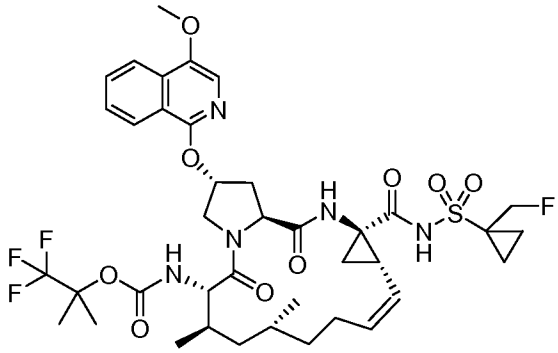


Compound 4154

Compound 4154 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4154: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4,6-dimethoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.07 (d, *J*=9.29 Hz, 1 H) 7.53 (s, 1 H) 7.44 (d, *J*=2.51 Hz, 1 H) 7.14 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.81 (br. s., 1 H) 5.57 - 5.68 (m, 1 H) 4.95 - 5.05 (m, 2 H) 4.77 - 4.84 (m, 2 H) 4.71 (d, *J*=11.29 Hz, 1 H) 4.59 - 4.66 (m, 2 H) 3.98 - 4.08 (m, 4 H) 3.95 (s, 3 H) 3.84 (d, *J*=10.79 Hz, 1 H) 3.28 (dt, *J*=3.33, 1.73 Hz, 1 H) 2.64 - 2.77 (m, 2 H) 2.43 (ddd, *J*=13.87, 10.23, 4.27 Hz, 2 H) 1.76 - 2.03 (m, 2 H) 1.62 - 1.76 (m, 2 H) 1.58 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.50 (d, *J*=8.78 Hz, 1 H) 1.36 - 1.43 (m, 3 H) 1.09 - 1.35 (m, 5 H) 0.94 - 1.06 (m, 7 H) 0.84 (t, *J*=11.54 Hz, 1 H) ; MS: MS *m/z* 868.7 (M^+-1).

Preparation of Compound 4155

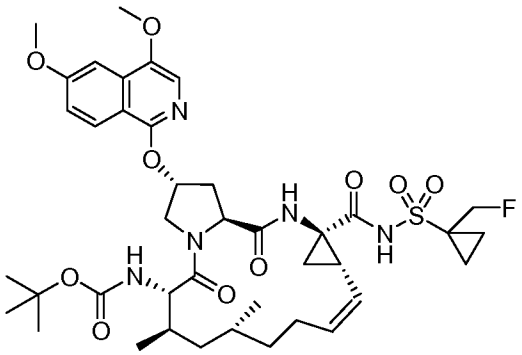


Compound 4155

Compound 4155 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4155: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.74 (t, *J*=7.65 Hz, 1 H) 7.54 - 7.60 (m, 2 H) 7.28 (d, *J*=8.03 Hz, 1 H) 5.84 (br. s., 1 H) 5.63 (d, *J*=6.02 Hz, 1 H) 5.00 (t, *J*=10.04 Hz, 2 H) 4.73 - 4.82 (m, 2 H) 4.62 - 4.68 (m, 2 H) 4.01 - 4.06 (m, 4 H) 3.81 - 3.87 (m, 1 H) 3.27 - 3.30 (m, 1 H) 2.68 - 2.78 (m, 3 H) 2.37 - 2.49 (m, 2 H) 1.97 (br. s., 1 H) 1.78 - 1.84 (m, 1 H) 1.69 - 1.75 (m, 2 H) 1.58 (dd, *J*=9.66, 5.65 Hz, 2 H) 1.43 - 1.54 (m, 2 H) 1.36 (s, 4 H) 1.16 - 1.33 (m, 3 H) 1.03 (d, *J*=7.03 Hz, 1 H) 0.95 - 1.01 (m, 7 H) 0.80 - 0.88 (m, 1 H) ; MS: MS *m/z* 838.6 (M^+-1).

Preparation of Compound 4156

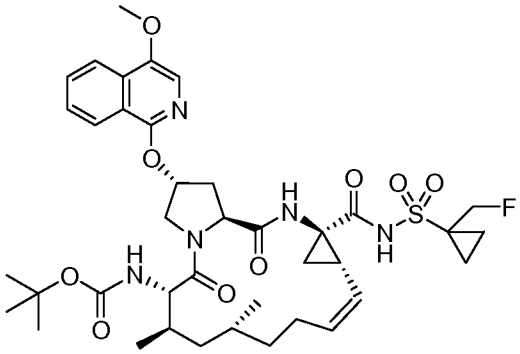


Compound 4156

Compound 4156 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4156: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4,6-dimethoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.07 (d, *J*=9.03 Hz, 1 H) 7.51 (s, 1 H) 7.42 (d, *J*=2.51 Hz, 1 H) 7.12 (dd, *J*=9.29, 2.51 Hz, 1 H) 5.81 (br. s., 1 H) 5.61 (dt, *J*=10.35, 5.24 Hz, 1 H) 4.96 - 5.05 (m, 1 H) 4.76 - 4.84 (m, 1 H) 4.63 - 4.72 (m, 1 H) 4.55 - 4.63 (m, 1 H) 4.51 (d, *J*=11.29 Hz, 1 H) 3.99 - 4.06 (m, 4 H) 3.85 - 3.96 (m, 4 H) 3.36 - 3.40 (m, 1 H) 3.28 (d, *J*=1.51 Hz, 1 H) 2.67 - 2.76 (m, 2 H) 2.36 - 2.48 (m, 2 H) 1.97 (br. s., 1 H) 1.76 - 1.90 (m, 2 H) 1.62 - 1.75 (m, 3 H) 1.56 (dd, *J*=9.41, 5.65 Hz, 1 H) 1.42 - 1.53 (m, 2 H) 1.20 - 1.35 (m, 4 H) 1.07 - 1.19 (m, 9 H) 1.01 (dd, *J*=14.18, 6.65 Hz, 3 H) 0.84 (t, *J*=11.54 Hz, 1 H) ; MS: MS *m/z* 816.4 (M^++1).

Preparation of Compound 4157

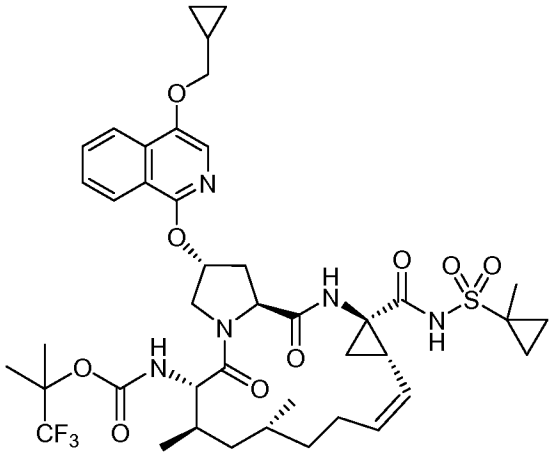


Compound 4157

Compound 4157 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4157: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(4-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.05 - 8.17 (m, 2 H) 7.70 (t, *J*=7.53 Hz, 1 H) 7.50 - 7.56 (m, 2 H) 6.59 (d, *J*=8.28 Hz, 1 H) 5.82 (br. s., 1 H) 5.59 (td, *J*=10.10, 5.65 Hz, 1 H) 4.91 - 5.01 (m, 1 H) 4.86 - 4.91 (m, 1 H) 4.73 - 4.79 (m, 1 H) 4.69 (d, *J*=11.29 Hz, 1 H) 4.54 - 4.63 (m, 2 H) 4.49 (d, *J*=11.29 Hz, 1 H) 3.97 - 4.05 (m, 4 H) 3.83 - 3.90 (m, 1 H) 3.25 (br. s., 1 H) 2.64 - 2.74 (m, 2 H) 2.35 - 2.45 (m, 2 H) 1.89 - 2.01 (m, 1 H) 1.74 - 1.87 (m, 2 H) 1.60 - 1.72 (m, 2 H) 1.40 - 1.57 (m, 3 H) 1.15 - 1.30 (m, 2 H) 1.11 (s, 9 H) 0.98 (dd, *J*=14.93, 6.65 Hz, 4 H) 0.77 - 0.85 (m, 1 H) ; MS: MS *m/z* 786.7 (M^++1).

Preparation of Compound 4158

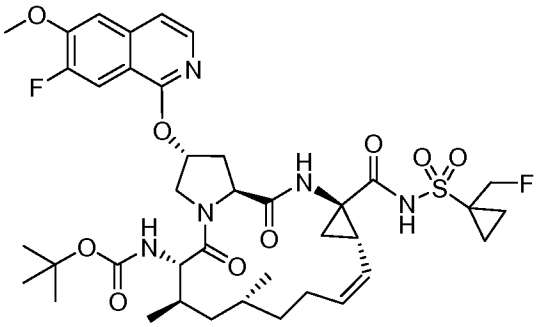


Compound 4158

Compound 4158 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4158: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-(cyclopropylmethoxy)isoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17 (dd, *J*=8.41, 4.39 Hz, 2 H) 7.72 - 7.79 (m, 1 H) 7.54 - 7.60 (m, 2 H) 7.29 (d, *J*=8.28 Hz, 1 H) 5.84 (br. s., 1 H) 5.62 (dt, *J*=10.42, 5.08 Hz, 1 H) 5.01 (t, *J*=9.79 Hz, 1 H) 4.74 - 4.82 (m, 2 H) 4.67 (dd, *J*=10.16, 7.15 Hz, 1 H) 3.99 - 4.06 (m, 3 H) 3.80 - 3.87 (m, 1 H) 3.29 (d, *J*=1.76 Hz, 2 H) 2.70 - 2.79 (m, 2 H) 2.44 (ddd, *J*=13.80, 10.04, 4.27 Hz, 2 H) 1.96 (d, *J*=13.55 Hz, 1 H) 1.81 - 1.91 (m, 1 H) 1.77 (dd, *J*=8.16, 5.65 Hz, 2 H) 1.66 (dd, *J*=9.54, 4.52 Hz, 1 H) 1.57 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.38 - 1.54 (m, 3 H) 1.17 - 1.38 (m, 5 H) 0.94 - 1.05 (m, 9 H) 0.86 - 0.93 (m, 2 H) 0.79 - 0.85 (m, 1 H) 0.67 - 0.73 (m, 2 H) 0.43 - 0.49 (m, 2 H) ; MS: MS *m/z* 861.0 (M^+-1).

Preparation of Compound 4159

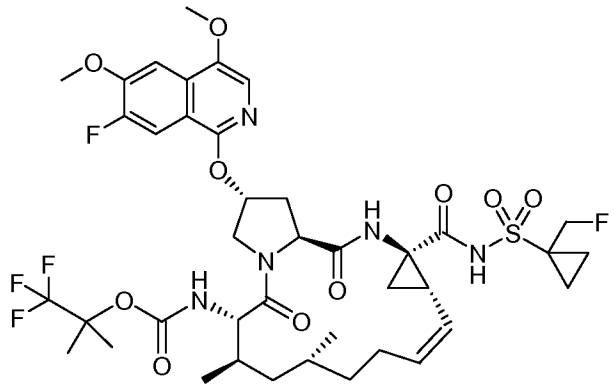


Compound 4159

Compound 4159 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4159: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.91 - 7.98 (m, 1 H) 7.78 (d, *J*=11.29 Hz, 1 H) 7.28 - 7.42 (m, 2 H) 6.67 (d, *J*=8.78 Hz, 1 H) 5.90 (br. s., 1 H) 5.63 (br. s., 1 H) 4.68 - 4.83 (m, 2 H) 4.48 - 4.66 (m, 2 H) 3.98 - 4.10 (m, 4 H) 3.81 - 3.97 (m, 1 H) 2.72 (d, *J*=7.53 Hz, 2 H) 2.38 - 2.50 (m, 2 H) 1.99 (d, *J*=16.31 Hz, 1 H) 1.85 (br. s., 2 H) 1.65 - 1.76 (m, 3 H) 1.58 (dd, *J*=9.66, 5.65 Hz, 1 H) 1.50 (d, *J*=7.03 Hz, 2 H) 1.31 (s, 3 H) 1.17 (s, 9 H) 1.02 (dd, *J*=11.54, 6.53 Hz, 7 H) 0.79 - 0.89 (m, 1 H) ; MS: MS *m/z* 802.4 (M^+-1).

Preparation of Compound 4160

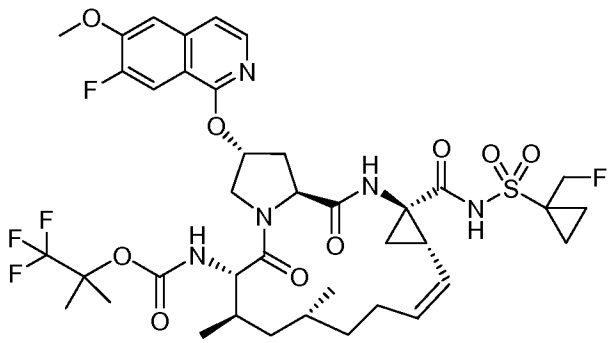


Compound 4160

Compound 4160 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4160: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.75 (d, *J*=11.54 Hz, 1 H) 7.53 - 7.60 (m, 2 H) 7.30 (d, *J*=7.78 Hz, 1 H) 5.82 (br. s., 1 H) 5.62 (dt, *J*=10.16, 4.96 Hz, 1 H) 5.00 (t, *J*=10.16 Hz, 1 H) 4.89 - 4.94 (m, 2 H) 4.76 - 4.82 (m, 2 H) 4.60 - 4.71 (m, 3 H) 3.97 - 4.05 (m, 7 H) 3.83 (dd, *J*=10.79, 8.03 Hz, 1 H) 3.28 (dt, *J*=3.26, 1.63 Hz, 2 H) 2.67 - 2.75 (m, 2 H) 2.36 - 2.48 (m, 2 H) 1.79 - 2.02 (m, 2 H) 1.64 - 1.75 (m, 2 H) 1.58 (dd, *J*=9.29, 5.52 Hz, 1 H) 1.50 (d, *J*=6.27 Hz, 2 H) 1.41 (s, 2 H) 1.18 - 1.33 (m, 3 H) 1.14 (s, 2 H) 1.02 (dd, *J*=11.29, 6.78 Hz, 5 H) 0.84 (t, *J*=12.30 Hz, 1 H) ; MS: MS *m/z* 888.2 (M^++1).

Preparation of Compound 4161

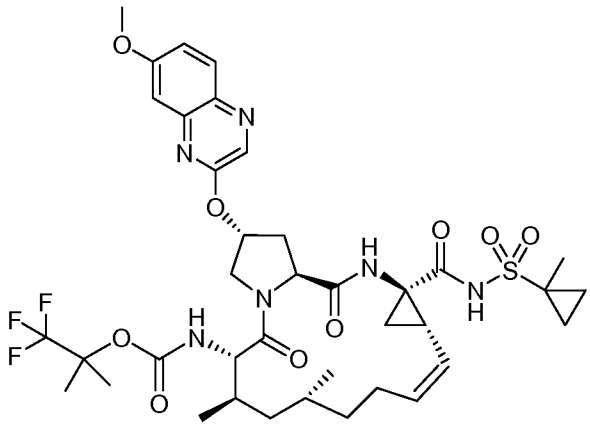


Compound 4161

Compound 4161 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 161: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.95 (d, *J*=5.77 Hz, 1 H) 7.79 (d, *J*=11.29 Hz, 1 H) 7.40 (d, *J*=8.28 Hz, 1 H) 7.31 (d, *J*=6.02 Hz, 2 H) 5.89 (s, 1 H) 5.63 (d, *J*=5.27 Hz, 1 H) 4.96 - 5.06 (m, 1 H) 4.61 - 4.76 (m, 3 H) 4.51 (d, *J*=11.54 Hz, 1 H) 4.00 - 4.07 (m, 4 H) 3.78 - 3.87 (m, 1 H) 3.25 - 3.30 (m, 2 H) 2.64 - 2.78 (m, 3 H) 2.46 (d, *J*=10.54 Hz, 2 H) 1.65 - 1.77 (m, 3 H) 1.58 (dd, *J*=10.04, 5.52 Hz, 1 H) 1.49 (s, 2 H) 1.40 (s, 3 H) 1.17 - 1.35 (m, 4 H) 1.14 (s, 3 H) 1.02 (dd, *J*=10.04, 6.78 Hz, 5 H) 0.82 - 0.92 (m, 1 H) ; MS: MS *m/z* 858.2 (M^++1).

Preparation of Compound 4162

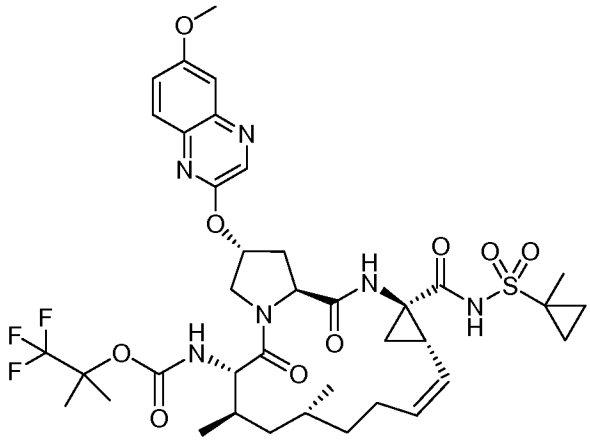


Compound 4162

Compound 4162 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4162: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-methoxyquinoxalin-2-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.27 (s, 1 H) 7.87 (d, *J*=9.29 Hz, 1 H) 7.26 - 7.40 (m, 3 H) 5.90 (br. s., 1 H) 5.63 (d, *J*=6.02 Hz, 1 H) 4.98 - 5.07 (m, 1 H) 4.76 (d, *J*=12.05 Hz, 1 H) 4.63 (dd, *J*=9.54, 7.28 Hz, 1 H) 4.08 (dd, *J*=11.54, 3.51 Hz, 1 H) 3.95 - 4.02 (m, 3 H) 3.81 (dd, *J*=10.54, 8.28 Hz, 1 H) 3.28 (dt, *J*=3.33, 1.73 Hz, 1 H) 2.65 - 2.76 (m, 3 H) 2.39 - 2.53 (m, 2 H) 1.85 - 2.04 (m, 2 H) 1.78 (dd, *J*=8.16, 5.65 Hz, 2 H) 1.64 - 1.71 (m, 1 H) 1.59 (dd, *J*=9.41, 5.65 Hz, 1 H) 1.38 - 1.55 (m, 3 H) 1.23 - 1.34 (m, 9 H) 0.99 (dd, *J*=19.32, 6.53 Hz, 5 H) 0.79 - 0.93 (m, 3 H) ; MS: MS *m/823.4* (M^++1).

Preparation of Compound 4163

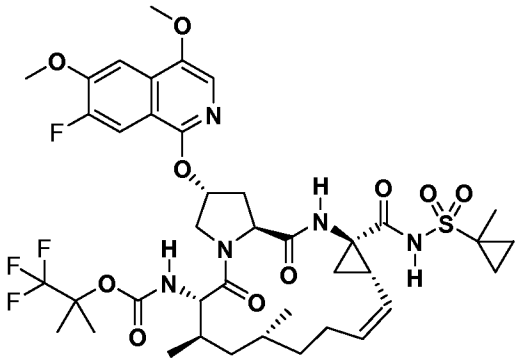


Compound 4163

Compound 4163 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4163: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(6-methoxyquinoxalin-2-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.41 (s, 1 H) 7.83 (d, *J*=9.29 Hz, 1 H) 7.33 - 7.46 (m, 2 H) 5.87 (br. s., 1 H) 5.63 (td, *J*=10.35, 5.90 Hz, 1 H) 4.98 - 5.06 (m, 1 H) 4.74 (d, *J*=11.54 Hz, 1 H) 4.63 (dd, *J*=9.91, 7.15 Hz, 1 H) 4.06 (dd, *J*=11.92, 3.39 Hz, 1 H) 3.93 - 3.98 (m, 3 H) 3.80 (d, *J*=11.04 Hz, 1 H) 3.27 - 3.30 (m, 1 H) 2.67 - 2.76 (m, 2 H) 2.39 - 2.52 (m, 2 H) 1.84 - 2.05 (m, 2 H) 1.78 (dd, *J*=8.41, 5.65 Hz, 2 H) 1.64 - 1.72 (m, 1 H) 1.59 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.40 - 1.55 (m, 6 H) 1.22 - 1.33 (m, 6 H) 0.94 - 1.05 (m, 6 H) 0.79 - 0.93 (m, 3 H) ; MS: MS *m/z* 823.4 (M^++1).

Preparation of Compound 4164

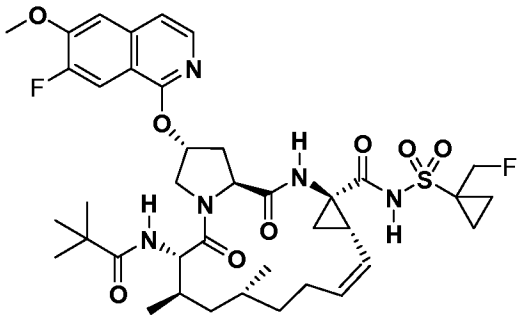


Compound 4164

Compound 4164 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4164: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.74 (d, *J*=11.54 Hz, 1 H) 7.52 - 7.60 (m, 2 H) 5.82 (br. s., 1 H) 5.62 (dt, *J*=10.29, 5.14 Hz, 1 H) 5.01 (t, *J*=9.91 Hz, 1 H) 4.59 - 4.72 (m, 2 H) 3.96 - 4.06 (m, 7 H) 3.82 (d, *J*=10.79 Hz, 1 H) 2.69 - 2.78 (m, 2 H) 2.36 - 2.50 (m, 2 H) 1.73 - 2.03 (m, 5 H) 1.62 - 1.69 (m, 1 H) 1.57 (dd, *J*=9.54, 5.52 Hz, 2 H) 1.46 - 1.53 (m, 3 H) 1.36 - 1.45 (m, 5 H) 1.31 (s, 2 H) 1.17 - 1.28 (m, 2 H) 1.13 (s, 2 H) 1.01 (t, *J*=6.90 Hz, 4 H) 0.80 - 0.94 (m, 3 H) ; MS: MS *m/z* 869.5 (M^++1).

Preparation of Compound 4165

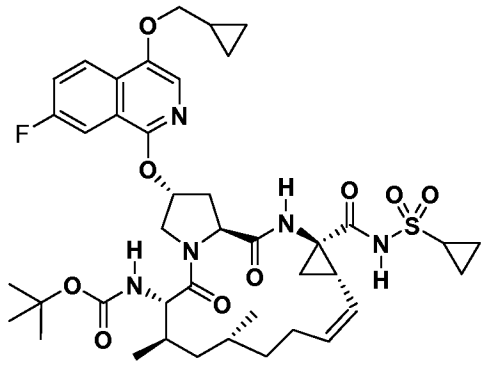


Compound 4165

Compound 4165 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4015.

Compound 4165: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-N-(1-(fluoromethyl)cyclopropylsulfonyl)-7,9-dimethyl-5,16-dioxo-6-pivalamido-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.99 (s, 1 H) 7.94 (d, *J*=6.02 Hz, 1 H) 7.78 (d, *J*=11.54 Hz, 1 H) 7.40 (d, *J*=8.28 Hz, 1 H) 7.32 (d, *J*=5.77 Hz, 1 H) 5.91 (br. s., 1 H) 5.58 - 5.68 (m, 1 H) 4.98 - 5.06 (m, 1 H) 4.76 - 4.82 (m, 1 H) 4.48 - 4.69 (m, 3 H) 4.21 - 4.29 (m, 1 H) 4.01 - 4.10 (m, 4 H) 2.67 - 2.78 (m, 2 H) 2.44 (ddd, *J*=13.93, 10.04, 4.14 Hz, 2 H) 1.95 - 2.10 (m, 2 H) 1.83 (dd, *J*=13.93, 5.90 Hz, 1 H) 1.62 - 1.75 (m, 3 H) 1.46 - 1.60 (m, 3 H) 1.14 - 1.33 (m, 4 H) 1.00 - 1.07 (m, 10 H) 0.97 (d, *J*=6.27 Hz, 3 H) 0.83 - 0.93 (m, 2 H) ; MS: MS *m/z* 789.3 (M^++1).

Preparation of Compound 4166

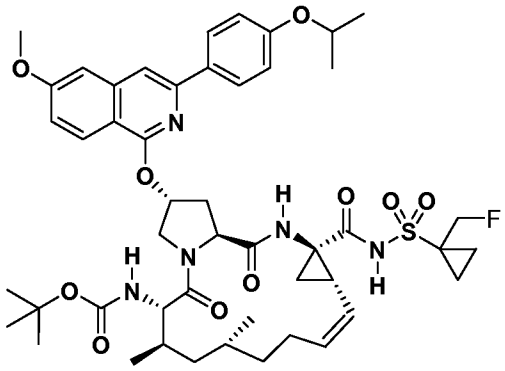


Compound 4166

Compound 4166 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4166: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-(cyclopropylmethoxy)-7-fluoroisoquinolin-1-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.22 (dd, *J*=9.03, 5.27 Hz, 1 H) 7.74 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.53 (s, 2 H) 5.83 (br. s., 1 H) 5.62 (d, *J*=6.02 Hz, 1 H) 5.06 (br. s., 1 H) 4.71 (d, *J*=11.29 Hz, 1 H) 4.55 - 4.66 (m, 2 H) 3.97 - 4.05 (m, 3 H) 3.81 - 3.88 (m, 1 H) 2.88 - 2.98 (m, 1 H) 2.72 (dd, *J*=14.43, 6.40 Hz, 2 H) 2.34 - 2.48 (m, 2 H) 1.97 (d, *J*=13.05 Hz, 1 H) 1.74 - 1.90 (m, 3 H) 1.59 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.44 - 1.55 (m, 2 H) 1.19 - 1.43 (m, 4 H) 1.06 - 1.18 (m, 9 H) 1.00 (dd, *J*=14.93, 6.65 Hz, 5 H) 0.83 (t, *J*=11.42 Hz, 1 H) 0.66 - 0.72 (m, 1 H) 0.44 (q, *J*=4.43 Hz, 2 H) ; MS: MS *m/z* 812.4 (M^++1).

Preparation of Compound 4167

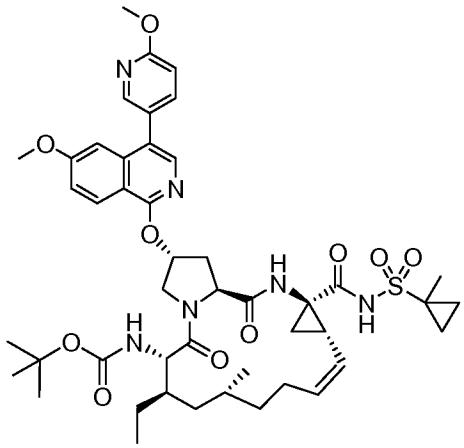


Compound 4167

Compound 4167 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4167: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.99 (s, 1 H) 8.05 - 8.14 (m, 4 H) 7.68 (s, 1 H) 7.23 (d, *J*=2.01 Hz, 1 H) 7.02 (d, *J*=8.78 Hz, 3 H) 6.09 (br. s., 1 H) 5.59 - 5.67 (m, 1 H) 5.01 (t, *J*=10.04 Hz, 2 H) 4.74 - 4.81 (m, 1 H) 4.58 - 4.73 (m, 3 H) 4.16 (dd, *J*=11.17, 3.64 Hz, 1 H) 3.90 - 3.99 (m, 4 H) 2.67 - 2.86 (m, 2 H) 2.38 - 2.56 (m, 2 H) 1.93 - 2.06 (m, 1 H) 1.79 - 1.92 (m, 2 H) 1.44 - 1.76 (m, 5 H) 1.37 (d, *J*=6.02 Hz, 4 H) 1.26 - 1.34 (m, 3 H) 1.18 - 1.24 (m, 9 H) 1.02 (dd, *J*=16.31, 6.78 Hz, 5 H) 0.82 - 0.94 (m, 2 H) ; MS: MS *m/z* 920.5 (M^++1).

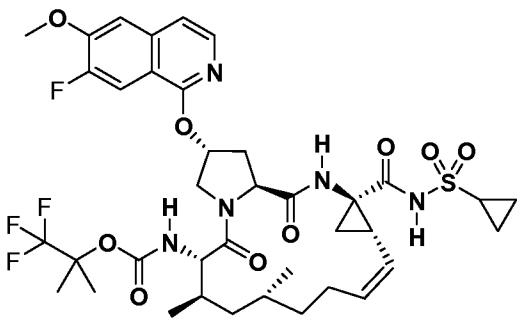
Preparation of Compound 4168



Compound 4168 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4168: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(6-methoxy-4-(6-methoxypyridin-3-yl)isoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.20 - 8.24 (m, 2 H) 7.88 (s, 1 H) 7.83 (dd, *J*=8.41, 2.38 Hz, 1 H) 7.17 (d, *J*=9.29 Hz, 1 H) 6.97 - 7.04 (m, 2 H) 5.93 (br. s., 1 H) 5.61 (br. s., 1 H) 4.66 (br. s., 1 H) 4.00 - 4.14 (m, 5 H) 3.81 - 3.85 (m, 3 H) 2.74 (br. s., 2 H) 2.38 - 2.55 (m, 2 H) 1.97 (br. s., 3 H) 1.78 (d, *J*=7.28 Hz, 1 H) 1.52 - 1.65 (m, 9 H) 1.29 - 1.36 (m, 4 H) 1.13 (s, 10 H) 1.01 (d, *J*=6.53 Hz, 3 H) 0.82 - 0.93 (m, 5 H). MS: MS *m/z* 890.07 (M^++1).

Preparation of Compound 4169

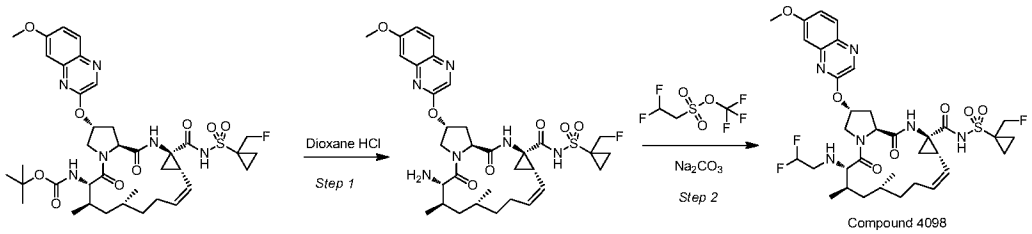


Compound 4169

Compound 4169 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4169: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.19 (dd, *J*=9.03, 5.52 Hz, 1 H) 7.76 (dd, *J*=9.41, 2.64 Hz, 1 H) 7.52 - 7.60 (m, 2 H) 7.30 (d, *J*=7.78 Hz, 1 H) 5.84 (br. s., 1 H) 5.63 (td, *J*=10.10, 5.90 Hz, 1 H) 5.01 - 5.10 (m, 1 H) 4.74 (d, *J*=11.54 Hz, 1 H) 4.56 - 4.69 (m, 1 H) 3.96 - 4.07 (m, 4 H) 3.79 - 3.87 (m, 1 H) 2.90 - 2.99 (m, 1 H) 2.68 - 2.79 (m, 2 H) 2.43 (ddd, *J*=13.87, 10.10, 4.14 Hz, 2 H) 1.75 - 2.04 (m, 4 H) 1.60 (dd, *J*=9.41, 5.65 Hz, 1 H) 1.43 - 1.56 (m, 2 H) 1.19 - 1.42 (m, 7 H) 1.08 - 1.18 (m, 2 H) 0.97 - 1.07 (m, 9 H) 0.84 (t, *J*=12.05 Hz, 1 H) ; MS: MS *m/z* 826.4 (M^++1).

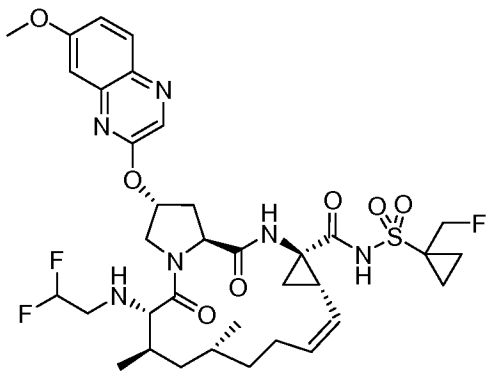
Scheme:



Step 1: Preparation of *(2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(1-(fluoromethyl)cyclopropylsulfonyl)-2-(7-methoxyquinoxalin-2-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride*

A solution of tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((7-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate (120 mg, 0.15 mmol) in 4M HCl in dioxane (10 ml 4 M solution) was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure to get crude compound (100 mg, 95%) as brown solid. The crude compound was washed with diethyl ether and taken to the next step without further purification. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.19 (s, 1 H) 8.26 - 8.34 (m, 2 H) 7.90 (d, *J*=8.78 Hz, 2 H) 7.26 - 7.34 (m, 3 H) 6.02 (br. s., 1 H) 5.58 - 5.67 (m, 1 H) 5.04 (t, *J*=9.54 Hz, 1 H) 4.59 - 4.71 (m, 2 H) 4.33 - 4.53 (m, 1 H) 4.12 - 4.26 (m, 2 H) 3.98 (s, 3 H) 3.73 - 3.81 (m, 2 H) 3.66 - 3.71 (m, 2 H) 2.77 - 2.97 (m, 2 H) 2.42 - 2.75 (m, 3 H) 1.91 - 2.11 (m, 2 H) 1.67 - 1.78 (m, 2 H) 1.44 - 1.62 (m, 2 H) 1.21 - 1.42 (m, 5 H) 1.01 - 1.15 (m, 5 H) 0.92 (br. s., 1 H): MS: MS *m/z* 687.4 (M^+-36).

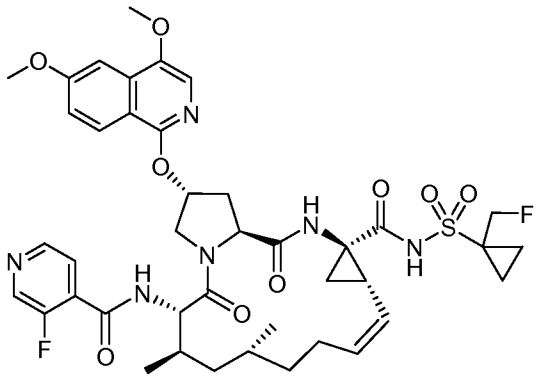
Step 2: Preparation of Compound 4170



Compound 4170

To a solution of (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-((1-(fluoromethyl)cyclopropyl)sulfonyl)-2-((7-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide (100 mg, 0.14 mmol) in DMF (1 ml) was added trifluoromethyl 2,2-difluoroethanesulfonate (31.2 mg, 0.14 mmol) followed by sodium carbonate (23.15 mg, 0.21 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The reaction mass was diluted with water and extracted with ethyl acetate and washed with brine solution. The combine organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC to get desired compound (15 mg, 13.5%) as white solid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.14 (s, 1 H) 8.28 (s, 1 H) 7.86 - 7.93 (m, 1 H) 7.25 - 7.34 (m, 2 H) 5.92 - 6.07 (m, 1 H) 5.64 (td, *J*=10.42, 5.52 Hz, 1 H) 5.04 (t, *J*=10.04 Hz, 1 H) 4.60 - 4.71 (m, 2 H) 4.51 (d, *J*=11.29 Hz, 1 H) 4.21 - 4.27 (m, 1 H) 4.11 - 4.17 (m, 1 H) 3.98 (s, 3 H) 3.04 - 3.12 (m, 1 H) 2.55 - 2.74 (m, 3 H) 2.38 - 2.49 (m, 1 H) 1.85 - 1.99 (m, 3 H) 1.64 - 1.78 (m, 3 H) 1.43 - 1.62 (m, 4 H) 1.19 - 1.36 (m, 4 H) 1.14 (d, *J*=6.53 Hz, 3 H) 1.05 (d, *J*=6.78 Hz, 3 H) 0.89 - 0.97 (m, 2 H); MS: MS *m/z* 751.2 (M^++1).

Preparation of Compound 4171

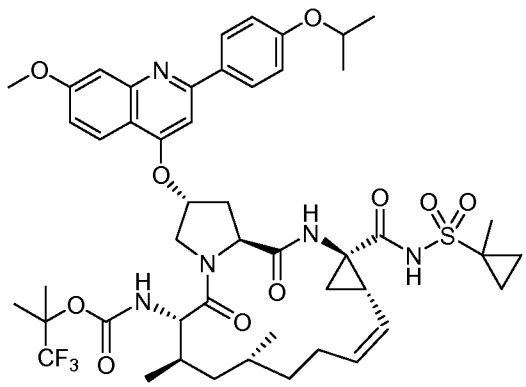


Compound 4171

Compound 4171 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4029.

Compound 4171: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4,6-dimethoxyisoquinolin-1-yloxy)-6-(3-fluoroisonicotinamido)-N-(1-(fluoromethyl)cyclopropylsulfonyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.05 (s, 1 H) 8.50 (s, 1 H) 8.34 (d, *J*=4.27 Hz, 1 H) 8.08 (d, *J*=9.03 Hz, 1 H) 7.51 (s, 1 H) 7.37 - 7.40 (m, 1 H) 7.15 (d, *J*=11.54 Hz, 1 H) 7.05 (t, *J*=5.40 Hz, 1 H) 5.87 (br. s., 1 H) 5.60 - 5.69 (m, 1 H) 4.99 - 5.05 (m, 1 H) 4.74 - 4.79 (m, 1 H) 4.63 - 4.69 (m, 2 H) 4.39 (d, *J*=11.29 Hz, 1 H) 4.08 - 4.13 (m, 1 H) 4.03 (s, 3 H) 3.95 (s, 3 H) 2.71 - 2.81 (m, 2 H) 2.43 - 2.53 (m, 2 H) 1.99 - 2.13 (m, 2 H) 1.81 - 1.89 (m, 1 H) 1.66 - 1.77 (m, 3 H) 1.50 - 1.61 (m, 3 H) 1.19 - 1.33 (m, 4 H) 1.05 (dd, *J*=6.65, 2.64 Hz, 8 H) 0.92 (t, *J*=12.17 Hz, 1 H). MS: MS *m/z* 840.2 (M^++1).

Preparation of Compound 4172



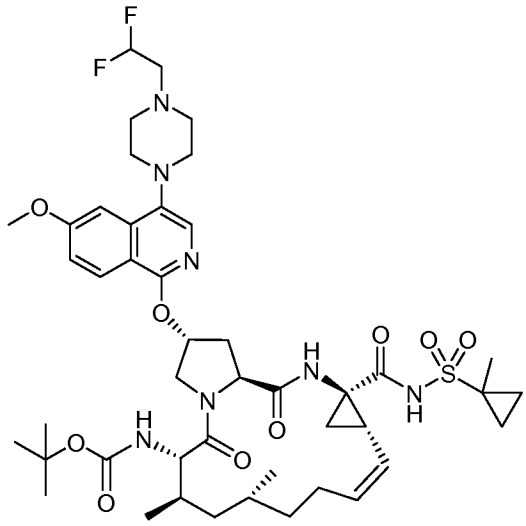
Compound 4172

Compound 4172 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4172: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(2-(4-isopropoxyphenyl)-7-methoxyquinolin-4-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.95 (d, *J*=6.27 Hz, 2 H) 7.79 (d, *J*=11.80 Hz, 2 H) 7.40 (d, *J*=8.03 Hz, 2 H) 7.30 (d, *J*=5.52 Hz, 2 H) 5.89 (br. s., 2 H) 4.03 (s, 6 H) 3.79 - 3.86 (m, 1 H) 2.70 (br. s., 3 H) 2.43 (s, 3 H) 2.00 (s, 3 H) 1.85 (br. s., 4 H) 1.71 - 1.80 (m, 2 H) 1.60 (s, 2 H) 1.48 (br. s., 4 H) 1.40 (s, 3 H) 1.28 - 1.34 (m, 6 H) 1.13 (s, 3 H) 1.01 (t, *J*=6.27 Hz, 6 H) 0.92 (s, 1 H).

MS: MS *m/z* 956 (M^++1).

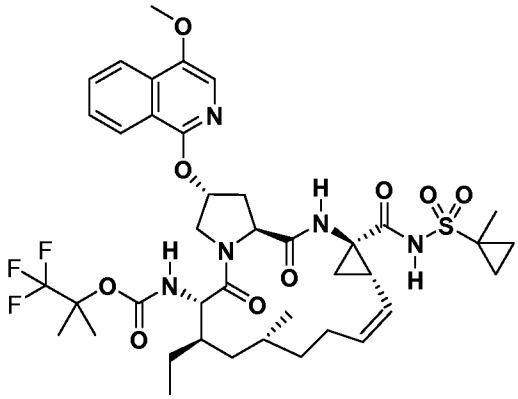
Preparation of Compound 4173



Compound 4173 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4173: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-(4-(2,2-difluoroethyl)piperazin-1-yl)-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-ethylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.12 (d, *J*=9.03 Hz, 1 H) 7.69 (s, 1 H) 7.41 (d, *J*=2.51 Hz, 1 H) 7.12 (dd, *J*=9.16, 2.38 Hz, 1 H) 5.84 (br. s., 1 H) 5.61 (br. s., 1 H) 4.71 (d, *J*=11.29 Hz, 1 H) 4.57 - 4.64 (m, 1 H) 4.04 (dd, *J*=11.42, 3.39 Hz, 1 H) 3.95 - 3.98 (m, 4 H) 3.88 (d, *J*=11.04 Hz, 1 H) 3.13 (m, 2 H) 2.91 (td, *J*=15.25, 4.39 Hz, 6 H) 2.72 (dd, *J*=12.80, 6.78 Hz, 2 H) 2.44 (d, *J*=9.79 Hz, 2 H) 1.99 (s, 1 H) 1.74 - 1.88 (m, 5 H) 1.40 - 1.59 (m, 9 H) 1.21 - 1.34 (m, 6 H) 1.15 (s, 8 H) 1.01 (dd, *J*=9.54, 6.78 Hz, 9 H) 0.80 - 0.92 (m, 4 H).MS: MS *m/z* 916.4 (M^++1).

Preparation of Compound 4174

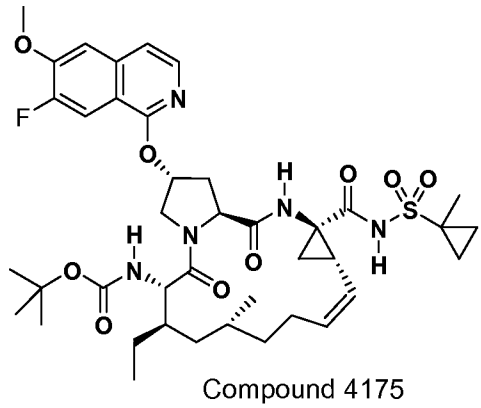


Compound 4174

Compound 4174 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4174: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(4-methoxyisoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.14 (dd, *J*=12.30, 8.28 Hz, 2 H) 7.74 (td, *J*=7.65, 1.25 Hz, 1 H) 7.55 - 7.61 (m, 2 H) 5.85 (br. s., 1 H) 5.57 - 5.67 (m, 1 H) 5.06 (br. s., 1 H) 4.75 - 4.82 (m, 2 H) 4.67 (dd, *J*=10.16, 7.15 Hz, 1 H) 4.00 - 4.10 (m, 5 H) 3.26 - 3.30 (m, 1 H) 2.66 - 2.79 (m, 2 H) 2.37 - 2.50 (m, 2 H) 1.92 - 2.06 (m, 3 H) 1.77 (dd, *J*=8.28, 5.52 Hz, 1 H) 1.54 - 1.70 (m, 5 H) 1.53 (s, 4 H) 1.40 - 1.48 (m, 2 H) 1.36 (s, 2 H) 1.25 - 1.33 (m, 2 H) 1.08 - 1.18 (m, 1 H) 1.02 (d, *J*=6.78 Hz, 2 H) 0.93 (s, 2 H) 0.88 (br. s., 2 H) 0.84 (t, *J*=7.53 Hz, 3 H) ; MS: MS *m/z* 836.6 (M^++1).

Preparation of Compound 4175

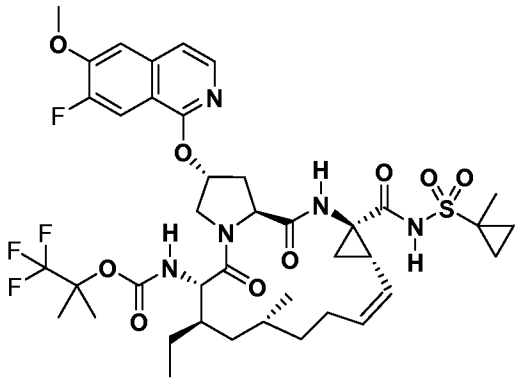


Compound 4175

Compound 4175 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4175: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.95 (d, *J*=5.77 Hz, 1 H) 7.77 (d, *J*=11.54 Hz, 1 H) 7.26 - 7.42 (m, 2 H) 6.62 (br. s., 1 H) 5.91 (br. s., 1 H) 5.62 (br. s., 1 H) 5.01 (br. s., 1 H) 4.75 (d, *J*=12.30 Hz, 1 H) 4.63 (br. s., 1 H) 3.97 - 4.14 (m, 5 H) 3.28 (dt, *J*=3.33, 1.73 Hz, 4 H) 2.65 - 2.80 (m, 2 H) 2.45 (br. s., 2 H) 1.98 (d, *J*=13.05 Hz, 2 H) 1.76 (br. s., 1 H) 1.48 - 1.69 (m, 6 H) 1.43 (d, *J*=9.79 Hz, 2 H) 1.23 - 1.37 (m, 1 H) 1.07 - 1.21 (m, 9 H) 1.02 (d, *J*=6.78 Hz, 3 H) 0.80 - 0.96 (m, 4 H) ; MS: MS *m/z* 800.7 (M^++1).

Preparation of Compound 4176

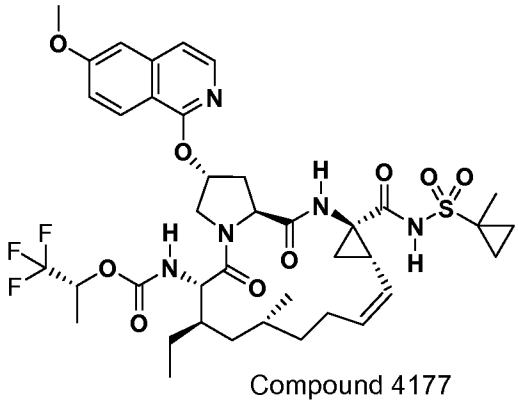


Compound 4176

Compound 4176 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4176: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.91 - 7.98 (m, 2 H) 7.78 (d, *J*=11.54 Hz, 1 H) 7.41 (d, *J*=8.28 Hz, 1 H) 7.30 - 7.34 (m, 1 H) 5.91 (br. s., 1 H) 5.58 - 5.67 (m, 1 H) 5.03 (t, *J*=10.04 Hz, 1 H) 4.77 - 4.80 (m, 2 H) 4.74 (d, *J*=11.54 Hz, 2 H) 4.66 (dd, *J*=10.16, 7.15 Hz, 1 H) 4.00 - 4.10 (m, 6 H) 3.49 - 3.56 (m, 1 H) 3.22 - 3.29 (m, 5 H) 2.39 - 2.49 (m, 2 H) 1.99 (br. s., 2 H) 1.77 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.54 - 1.69 (m, 3 H) 1.53 (s, 3 H) 1.38 - 1.47 (m, 3 H) 1.20 - 1.34 (m, 2 H) 1.07 - 1.19 (m, 2 H) 1.02 (d, *J*=6.78 Hz, 3 H) 0.87 - 0.94 (m, 3 H) 0.84 (t, *J*=7.53 Hz, 3 H) ; MS: MS *m/z* 854.6 (M^++1).

Preparation of Compound 4177

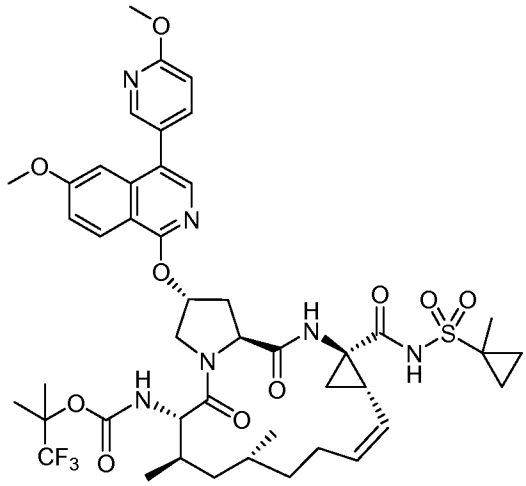


Compound 4177

Compound 4177 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4177: (R)-1,1,1-trifluoropropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(6-methoxyisoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.06 (d, *J*=9.03 Hz, 1 H) 7.92 (d, *J*=5.77 Hz, 1 H) 7.18 - 7.31 (m, 2 H) 7.08 (dd, *J*=9.16, 2.38 Hz, 1 H) 5.90 (br. s., 1 H) 5.63 (d, *J*=6.02 Hz, 1 H) 4.97 - 5.10 (m, 1 H) 4.73 - 4.82 (m, 2 H) 4.63 (dd, *J*=10.04, 7.28 Hz, 1 H) 4.45 - 4.58 (m, 1 H) 3.98 - 4.16 (m, 2 H) 3.89 - 3.96 (m, 3 H) 3.29 (d, *J*=1.76 Hz, 1 H) 2.67 - 2.81 (m, 2 H) 2.38 - 2.51 (m, 2 H) 1.94 - 2.09 (m, 2 H) 1.76 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.55 - 1.70 (m, 5 H) 1.39 - 1.53 (m, 5 H) 1.24 - 1.38 (m, 2 H) 1.10 - 1.23 (m, 3 H) 1.02 (d, *J*=6.78 Hz, 3 H) 0.87 - 0.95 (m, 3 H) 0.84 (t, *J*=7.53 Hz, 3 H) ; MS: MS *m/z* 822.6 (M^++1).

Preparation of Compound 4178

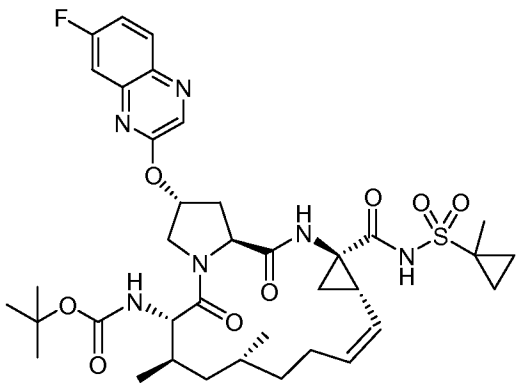


Compound 4178

Compound 4178 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4178: 1,1,1-trifluoro-2-methylpropan-2-yl(2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(6-methoxy-4-(6-methoxypyridin-3-yl)isoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.20 - 8.24 (m, 2 H) 7.89 (s, 1 H) 7.83 (dd, *J*=8.53, 2.51 Hz, 1 H) 7.19 (dd, *J*=9.16, 2.38 Hz, 1 H) 6.98 - 7.05 (m, 2 H) 5.93 (br. s., 1 H) 5.62 (br. s., 1 H) 4.96 - 5.08 (m, 1 H) 4.82 (d, *J*=12.05 Hz, 1 H) 4.70 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.00 - 4.08 (m, 4 H) 3.80 - 3.87 (m, 4 H) 2.79 (dd, *J*=13.80, 7.28 Hz, 2 H) 2.40 - 2.53 (m, 2 H) 1.75 - 2.03 (m, 3 H) 1.51 - 1.61 (m, 5 H) 1.36 - 1.50 (m, 6 H) 1.20 - 1.32 (m, 2 H) 1.01 (t, *J*=7.91 Hz, 9 H) 0.80 - 0.94 (m, 3 H).MS: MS *m/z* 929.4 (M^++1).

Preparation of Compound 4179

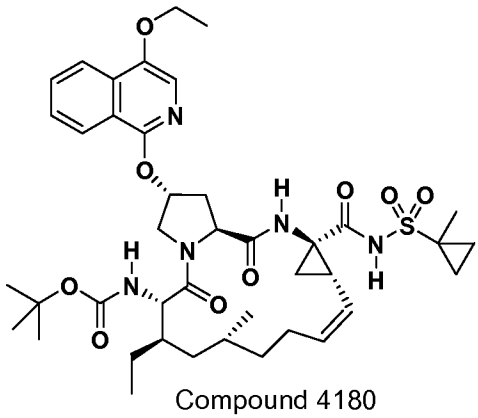


Compound 4179

Compound 4179 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4179: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoroquinoxalin-2-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.41 (s, 1 H) 8.02 (dd, *J*=9.16, 5.90 Hz, 1 H) 7.58 (dd, *J*=9.66, 2.89 Hz, 1 H) 7.46 (td, *J*=8.66, 2.76 Hz, 1 H) 5.88 (br. s., 1 H) 5.53 (br. s., 1 H) 4.70 (d, *J*=11.54 Hz, 1 H) 4.56 (t, *J*=8.41 Hz, 1 H) 4.09 (dd, *J*=11.80, 3.51 Hz, 1 H) 3.83 (d, *J*=10.79 Hz, 1 H) 3.00 (q, *J*=7.28 Hz, 3 H) 2.91 (d, *J*=7.03 Hz, 2 H) 2.70 (dd, *J*=13.93, 7.40 Hz, 1 H) 2.45 - 2.57 (m, 1 H) 2.37 (br. s., 1 H) 1.95 - 2.05 (m, 1 H) 1.69 - 1.89 (m, 3 H) 1.38 - 1.57 (m, 6 H) 1.29 (t, *J*=7.28 Hz, 4 H) 1.21 (t, *J*=7.28 Hz, 1 H) 1.13 (s, 6 H) 0.94 - 1.02 (m, 5 H) 0.72 - 0.84 (m, 2 H). MS: MS *m/z* 757.4 (M^++1).

Preparation of Compound 4180

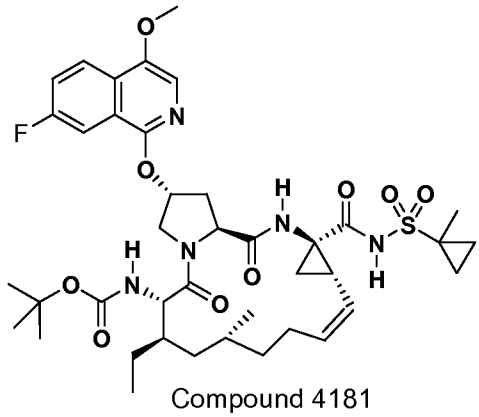


Compound 4180

Compound 4180 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4180: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxyisoquinolin-1-yloxy)-7-ethyl-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.10 - 8.19 (m, 2 H) 7.73 (t, *J*=7.28 Hz, 1 H) 7.51 - 7.60 (m, 2 H) 6.62 (d, *J*=8.78 Hz, 1 H) 5.85 (br. s., 1 H) 5.63 (td, *J*=10.04, 5.77 Hz, 1 H) 5.01 (t, *J*=9.79 Hz, 1 H) 4.78 (d, *J*=11.80 Hz, 1 H) 4.63 (dd, *J*=9.91, 7.15 Hz, 1 H) 4.24 (q, *J*=7.03 Hz, 2 H) 4.01 - 4.17 (m, 2 H) 3.28 (br. s., 2 H) 2.68 - 2.81 (m, 2 H) 2.43 (ddd, *J*=13.87, 10.10, 4.14 Hz, 2 H) 1.91 - 2.05 (m, 2 H) 1.77 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.63 - 1.71 (m, 1 H) 1.48 - 1.62 (m, 9 H) 1.42 (s, 2 H) 1.31 (s, 2 H) 1.13 (s, 9 H) 1.02 (d, *J*=6.78 Hz, 3 H) 0.90 (d, *J*=2.51 Hz, 3 H) 0.82 - 0.87 (m, 3 H) ; MS: MS *m/z* 796.7 (M^++1).

Preparation of Compound 4181

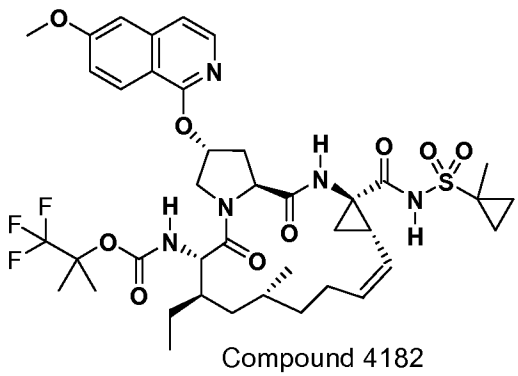


Compound 4181

Compound 4181 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4181: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.18 (dd, *J*=9.16, 5.40 Hz, 1 H) 7.74 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.50 - 7.60 (m, 2 H) 6.62 (d, *J*=8.78 Hz, 1 H) 5.86 (br. s., 1 H) 5.57 - 5.68 (m, 1 H) 5.02 (br. s., 1 H) 4.77 (d, *J*=11.80 Hz, 2 H) 4.64 (dd, *J*=10.04, 7.28 Hz, 1 H) 4.00 - 4.13 (m, 4 H) 3.38 (br. s., 2 H) 3.22 - 3.26 (m, 3 H) 2.73 (t, *J*=7.91 Hz, 2 H) 2.45 (d, *J*=9.79 Hz, 1 H) 1.97 (d, *J*=11.80 Hz, 2 H) 1.77 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.66 (d, *J*=10.54 Hz, 1 H) 1.47 - 1.62 (m, 5 H) 1.39 - 1.47 (m, 2 H) 1.22 - 1.34 (m, 2 H) 1.06 - 1.19 (m, 9 H) 1.02 (d, *J*=6.78 Hz, 3 H) 0.90 (br. s., 1 H) 0.85 (t, *J*=7.40 Hz, 3 H) ; MS: MS *m/z* 800.7 (M^++1).

Preparation of Compound 4182

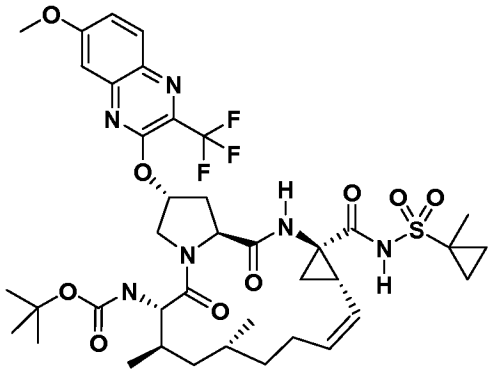


Compound 4182

Compound 4182 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4182: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(6-methoxyisoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.09 (d, *J*=9.29 Hz, 1 H) 7.94 (d, *J*=6.02 Hz, 1 H) 7.26 - 7.32 (m, 2 H) 7.22 (d, *J*=2.51 Hz, 1 H) 7.12 (dd, *J*=9.16, 2.38 Hz, 1 H) 5.90 (br. s., 1 H) 5.63 (td, *J*=10.10, 6.15 Hz, 1 H) 5.02 (t, *J*=9.91 Hz, 1 H) 4.91 (s, 1 H) 4.77 - 4.81 (m, 2 H) 4.76 (br. s., 1 H) 4.67 (dd, *J*=10.16, 7.15 Hz, 1 H) 4.01 - 4.11 (m, 2 H) 3.95 (s, 3 H) 3.29 (dd, *J*=3.26, 1.51 Hz, 2 H) 2.70 - 2.79 (m, 2 H) 2.40 - 2.49 (m, 2 H) 1.99 (t, *J*=11.54 Hz, 2 H) 1.77 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.66 (dd, *J*=9.54, 4.52 Hz, 1 H) 1.58 (dd, *J*=9.41, 5.65 Hz, 2 H) 1.53 (s, 2 H) 1.41 - 1.47 (m, 2 H) 1.39 (s, 2 H) 1.23 - 1.34 (m, 2 H) 1.14 (s, 1 H) 0.97 - 1.04 (m, 5 H) 0.88 - 0.92 (m, 2 H) 0.84 (t, *J*=7.40 Hz, 3 H) ; MS: MS *m/z* 836.6 (M^++1).

Preparation of Compound 4183

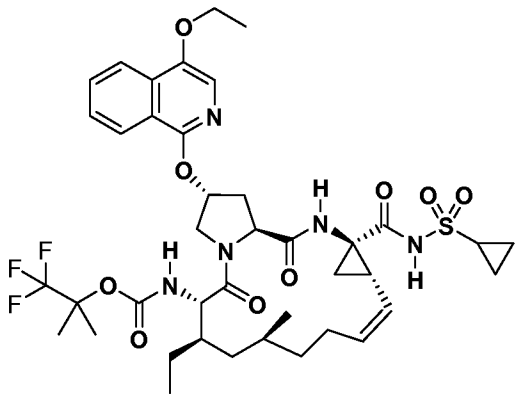


Compound 4183

Compound 4183 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4183: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-methoxy-3-(trifluoromethyl)quinoxalin-2-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.97 (d, *J*=10.04 Hz, 1 H) 7.34 - 7.40 (m, 2 H) 5.98 (br. s., 1 H) 5.59 (br. s., 1 H) 4.81 (br. s., 1 H) 4.59 - 4.65 (m, 1 H) 4.02 - 4.09 (m, 4 H) 3.78 (d, *J*=10.79 Hz, 1 H) 2.68 (br. s., 2 H) 2.42 - 2.54 (m, 2 H) 1.98 (s, 3 H) 1.75 - 1.87 (m, 3 H) 1.51 - 1.60 (m, 5 H) 1.44 (d, *J*=16.06 Hz, 3 H) 1.22 - 1.36 (m, 3 H) 1.07 - 1.10 (m, 8 H) 0.95 - 1.03 (m, 6 H) 0.79 - 0.88 (m, 1 H). . MS: MS *m/z* 837.5 (M^++1).

Preparation of Compound 4184

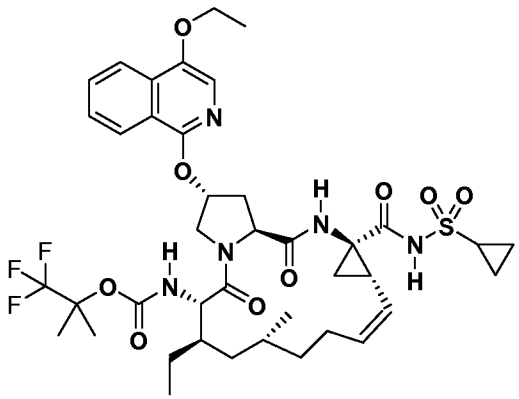


Compound 4184

Compound 4184 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4184: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(4-ethoxyisoquinolin-1-yloxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.16 (dd, *J*=12.67, 8.16 Hz, 2 H) 7.72 - 7.77 (m, 1 H) 7.55 - 7.60 (m, 2 H) 5.84 (br. s., 1 H) 5.73 (d, *J*=9.29 Hz, 1 H) 5.08 (br. s., 1 H) 4.81 (br. s., 2 H) 4.68 - 4.74 (m, 1 H) 4.60 (d, *J*=11.04 Hz, 1 H) 4.30 (d, *J*=6.78 Hz, 1 H) 4.25 (q, *J*=7.03 Hz, 2 H) 4.01 - 4.09 (m, 1 H) 3.29 (d, *J*=1.76 Hz, 4 H) 2.93 (br. s., 1 H) 2.73 (dd, *J*=12.55, 7.28 Hz, 1 H) 2.48 (d, *J*=9.79 Hz, 2 H) 2.03 (br. s., 1 H) 1.91 (br. s., 1 H) 1.70 - 1.77 (m, 1 H) 1.63 (br. s., 2 H) 1.55 (t, *J*=6.90 Hz, 4 H) 1.46 - 1.51 (m, 1 H) 1.44 (s, 4 H) 1.30 - 1.40 (m, 5 H) 1.12 (s, 3 H) 0.97 - 1.01 (m, 2 H) 0.92 - 0.97 (m, 3 H) ; MS: MS *m/z* 836.5 (M^++1).

Preparation of Compound 4185

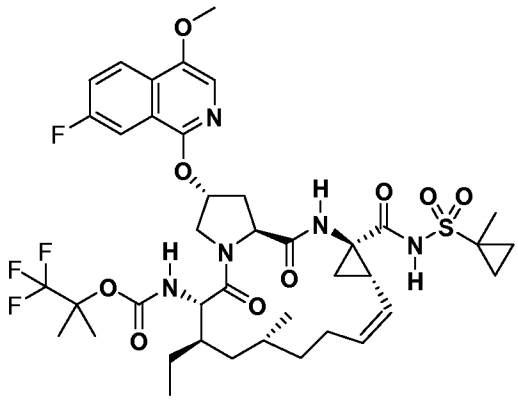


Compound 4185

Compound 4185 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4185: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(4-ethoxyisoquinolin-1-yloxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.15 (d, *J*=9.29 Hz, 2 H) 7.74 (t, *J*=7.15 Hz, 1 H) 7.54 - 7.60 (m, 2 H) 5.84 (br. s., 1 H) 5.63 (d, *J*=6.02 Hz, 1 H) 5.05 (br. s., 1 H) 4.76 - 4.81 (m, 4 H) 4.63 - 4.70 (m, 1 H) 4.25 (q, *J*=7.03 Hz, 2 H) 3.98 - 4.10 (m, 2 H) 3.24 - 3.28 (m, 2 H) 2.94 (br. s., 1 H) 2.70 - 2.79 (m, 2 H) 2.38 - 2.48 (m, 1 H) 1.97 (d, *J*=10.29 Hz, 2 H) 1.74 - 1.82 (m, 1 H) 1.50 - 1.63 (m, 6 H) 1.47 (br. s., 1 H) 1.30 - 1.39 (m, 4 H) 1.28 (br. s., 1 H) 1.06 - 1.19 (m, 3 H) 1.03 (d, *J*=6.53 Hz, 4 H) 0.93 (s, 2 H) 0.83 (t, *J*=7.40 Hz, 3 H) ; MS: MS *m/z* 836.5 (M^++1).

Preparation of Compound 4186

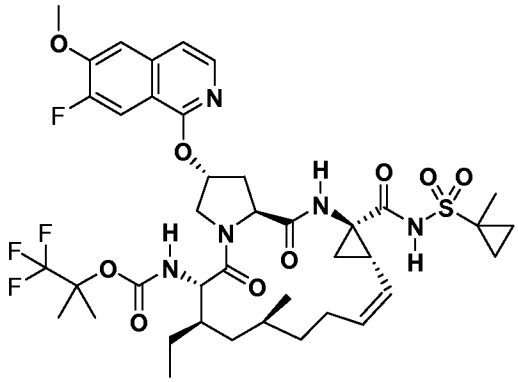


Compound 4186

Compound 4186 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4186: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.19 (dd, *J*=9.16, 5.40 Hz, 1 H) 7.75 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.52 - 7.60 (m, 2 H) 5.85 (br. s., 1 H) 5.63 (d, *J*=5.02 Hz, 1 H) 5.01 (d, *J*=12.05 Hz, 1 H) 4.77 (d, *J*=12.05 Hz, 1 H) 4.61 - 4.69 (m, 1 H) 3.99 - 4.08 (m, 5 H) 3.23 - 3.27 (m, 2 H) 2.72 - 2.79 (m, 2 H) 2.40 - 2.49 (m, 2 H) 1.93 - 2.04 (m, 2 H) 1.77 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.64 (br. s., 1 H) 1.55 - 1.63 (m, 4 H) 1.53 (s, 4 H) 1.43 (dd, *J*=9.91, 4.89 Hz, 2 H) 1.37 (s, 3 H) 1.20 - 1.34 (m, 3 H) 1.14 (t, *J*=13.05 Hz, 1 H) 0.99 - 1.05 (m, 5 H) 0.89 (br. s., 2 H) 0.84 (t, *J*=7.53 Hz, 3 H) ; MS: MS *m/z* 854.5 (M^++1).

Preparation of Compound 4187

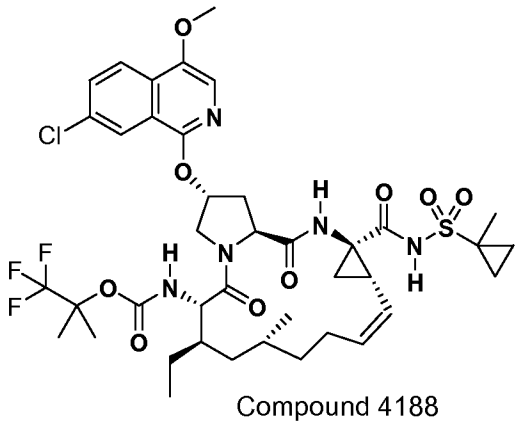


Compound 4187

Compound 4187 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4187: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.95 (d, *J*=5.77 Hz, 1 H) 7.83 (d, *J*=11.80 Hz, 1 H) 7.40 (d, *J*=8.28 Hz, 1 H) 7.31 (d, *J*=5.77 Hz, 1 H) 7.25 - 7.29 (m, 1 H) 5.91 (br. s., 1 H) 5.75 (d, *J*=10.04 Hz, 1 H) 5.04 (br. s., 1 H) 4.72 (dd, *J*=9.79, 7.28 Hz, 1 H) 4.56 (d, *J*=11.54 Hz, 1 H) 4.31 (d, *J*=5.27 Hz, 1 H) 4.01 - 4.07 (m, 4 H) 2.73 (dd, *J*=14.43, 7.15 Hz, 1 H) 2.61 (d, *J*=9.29 Hz, 1 H) 2.40 - 2.52 (m, 2 H) 1.95 - 2.07 (m, 1 H) 1.88 (br. s., 1 H) 1.71 (dd, *J*=8.16, 5.65 Hz, 1 H) 1.56 - 1.67 (m, 4 H) 1.52 (s, 3 H) 1.48 (s, 3 H) 1.39 - 1.46 (m, 3 H) 1.30 - 1.37 (m, 1 H) 1.28 (s, 3 H) 1.10 (s, 1 H) 0.97 - 1.05 (m, 2 H) 0.93 (d, *J*=6.78 Hz, 3 H) 0.82 - 0.91 (m, 3 H) ; MS: MS *m/z* 854.4 (M^++1).

Preparation of Compound 4188

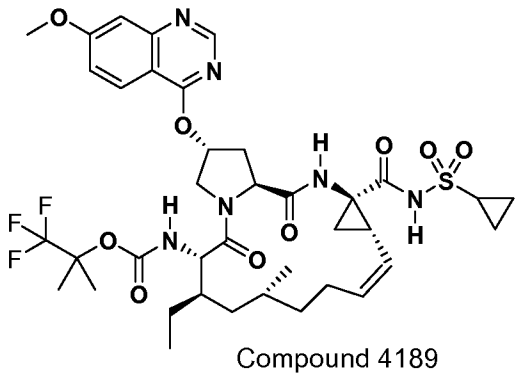


Compound 4188

Compound 4188 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4188: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-chloro-4-methoxyisoquinolin-1-yloxy)-7-ethyl-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.06 - 8.15 (m, 2 H) 7.72 (dd, *J*=8.91, 2.13 Hz, 1 H) 7.64 (s, 1 H) 7.30 (d, *J*=8.78 Hz, 1 H) 5.88 (s, 1 H) 5.63 (d, *J*=5.52 Hz, 1 H) 5.02 (t, *J*=9.29 Hz, 1 H) 4.67 - 4.80 (m, 2 H) 3.98 - 4.06 (m, 5 H) 3.38 - 3.42 (m, 1 H) 2.70 - 2.79 (m, 2 H) 2.45 (t, *J*=9.66 Hz, 2 H) 1.98 (br. s., 2 H) 1.74 - 1.81 (m, 1 H) 1.67 (d, *J*=11.54 Hz, 1 H) 1.51 - 1.63 (m, 8 H) 1.39 - 1.47 (m, 2 H) 1.27 - 1.33 (m, 3 H) 1.07 - 1.23 (m, 1 H) 1.02 (d, *J*=6.78 Hz, 3 H) 0.87 - 0.94 (m, 5 H) 0.83 (t, *J*=7.28 Hz, 3 H) ; MS: MS *m/z* 870.2 (M^++1).

Preparation of Compound 4189

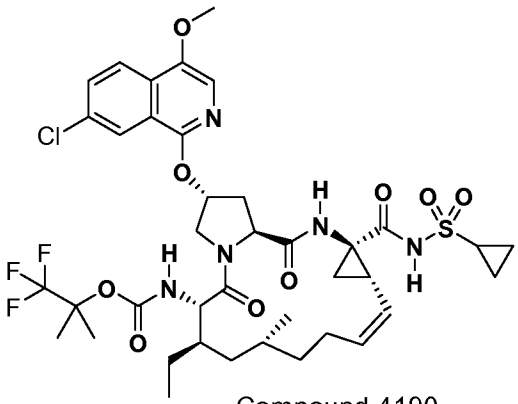


Compound 4189

Compound 4189 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4189: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-7-ethyl-2-(7-methoxyquinazolin-4-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.75 (br. s., 1 H) 8.07 (d, *J*=5.77 Hz, 1 H) 7.26 (d, *J*=17.07 Hz, 2 H) 6.00 (br. s., 1 H) 5.63 (br. s., 1 H) 5.06 (br. s., 1 H) 4.56 - 4.73 (m, 1 H) 3.96 - 4.10 (m, 5 H) 3.24 - 3.30 (m, 1 H) 3.16 (br. s., 1 H) 2.94 (br. s., 1 H) 2.66 - 2.84 (m, 2 H) 2.34 - 2.55 (m, 2 H) 1.99 (br. s., 2 H) 1.80 (br. s., 1 H) 1.57 (d, *J*=17.82 Hz, 5 H) 1.33 (br. s., 7 H) 0.97 - 1.19 (m, 7 H) 0.94 (br. s., 3 H) 0.82 (br. s., 3 H) ; MS: MS *m/z* 821.5 (M^+-1).

Preparation of Compound 4190

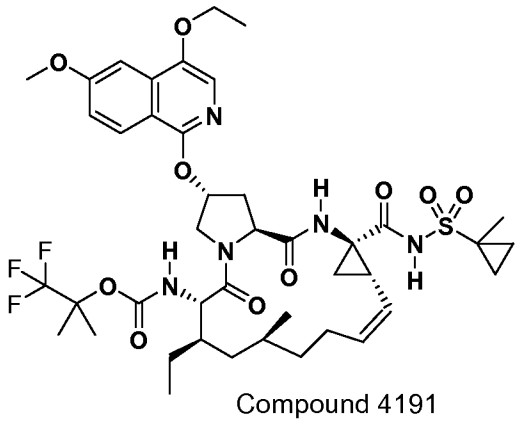


Compound 4190

Compound 4190 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4190: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-chloro-4-methoxyisoquinolin-1-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.06 - 8.16 (m, 2 H) 7.72 (dd, *J*=8.78, 2.26 Hz, 1 H) 7.64 (s, 1 H) 7.29 (d, *J*=8.53 Hz, 1 H) 5.88 (br. s., 1 H) 5.58 - 5.67 (m, 1 H) 5.05 (t, *J*=10.04 Hz, 1 H) 4.74 - 4.82 (m, 1 H) 4.70 (dd, *J*=10.54, 7.28 Hz, 1 H) 3.97 - 4.06 (m, 5 H) 3.29 (dd, *J*=3.39, 1.63 Hz, 1 H) 2.95 (br. s., 1 H) 2.69 - 2.78 (m, 2 H) 2.39 - 2.50 (m, 2 H) 1.93 - 2.05 (m, 2 H) 1.79 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.46 - 1.64 (m, 7 H) 1.30 - 1.46 (m, 4 H) 1.21 - 1.30 (m, 3 H) 1.06 - 1.18 (m, 2 H) 1.03 (d, *J*=6.78 Hz, 3 H) 0.92 (s, 3 H) 0.83 (t, *J*=7.40 Hz, 2 H) ; MS: MS *m/z* 857.5 (M^++1).

Preparation of Compound 4191

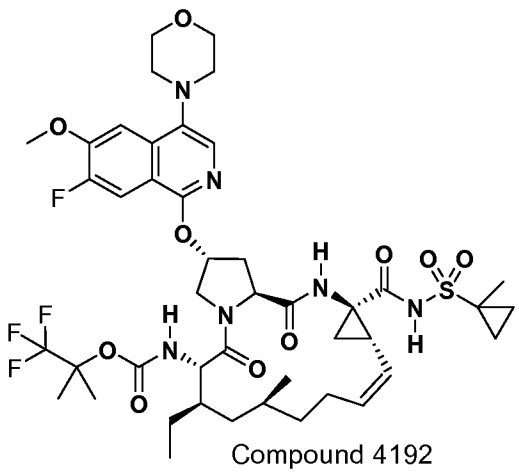


Compound 4191

Compound 4191 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4191: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-(4-ethoxy-6-methoxyisoquinolin-1-yloxy)-7-ethyl-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.08 (d, *J*=9.29 Hz, 1 H) 7.52 (s, 1 H) 7.45 (d, *J*=2.26 Hz, 1 H) 7.15 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.82 (br. s., 1 H) 5.74 (d, *J*=9.03 Hz, 1 H) 5.05 (br. s., 1 H) 4.67 - 4.74 (m, 1 H) 4.55 (d, *J*=11.54 Hz, 1 H) 4.31 (d, *J*=6.78 Hz, 1 H) 4.24 (q, *J*=6.86 Hz, 2 H) 4.04 (d, *J*=11.04 Hz, 1 H) 3.96 (s, 3 H) 2.71 (dd, *J*=13.30, 7.28 Hz, 1 H) 2.60 (br. s., 1 H) 2.40 - 2.52 (m, 2 H) 1.96 - 2.09 (m, 1 H) 1.89 (br. s., 1 H) 1.69 - 1.75 (m, 1 H) 1.60 (d, *J*=8.53 Hz, 5 H) 1.53 - 1.58 (m, 5 H) 1.52 (s, 3 H) 1.38 - 1.48 (m, 5 H) 1.30 - 1.36 (m, 3 H) 1.20 (s, 3 H) 0.99 (t, *J*=7.40 Hz, 3 H) 0.93 (d, *J*=6.78 Hz, 3 H) 0.89 (br. s., 2 H) ; MS: MS *m/z* 880.4 (M^++1).

Preparation of Compound 4192

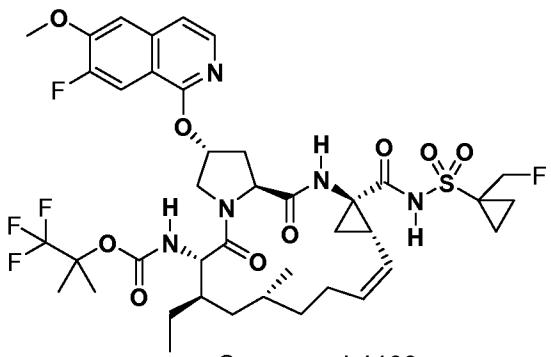


Compound 4192

Compound 4192 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4192: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-(7-fluoro-6-methoxy-4-morpholinoisoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.82 (d, *J*=11.54 Hz, 1 H) 7.74 (s, 1 H) 7.60 (d, *J*=8.28 Hz, 1 H) 5.86 (br. s., 1 H) 5.70 - 5.79 (m, 1 H) 5.05 (br. s., 1 H) 4.71 (dd, *J*=9.79, 7.28 Hz, 2 H) 4.54 (d, *J*=11.54 Hz, 1 H) 4.31 (d, *J*=6.27 Hz, 1 H) 4.01 - 4.09 (m, 5 H) 3.93 - 3.99 (m, 5 H) 3.06 - 3.12 (m, 4 H) 2.71 (dd, *J*=13.30, 7.53 Hz, 1 H) 2.59 (br. s., 1 H) 2.40 - 2.50 (m, 2 H) 2.00 (t, *J*=7.53 Hz, 1 H) 1.87 (br. s., 1 H) 1.72 (dd, *J*=8.03, 5.52 Hz, 1 H) 1.56 - 1.68 (m, 4 H) 1.49 - 1.54 (m, 4 H) 1.40 - 1.49 (m, 3 H) 1.30 - 1.39 (m, 3 H) 1.27 (s, 3 H) 1.00 (t, *J*=7.40 Hz, 3 H) 0.93 (d, *J*=6.78 Hz, 3 H) 0.89 (br. s., 2 H) ; MS: MS *m/z* 939.4 (M^++1).

Preparation of Compound 4193

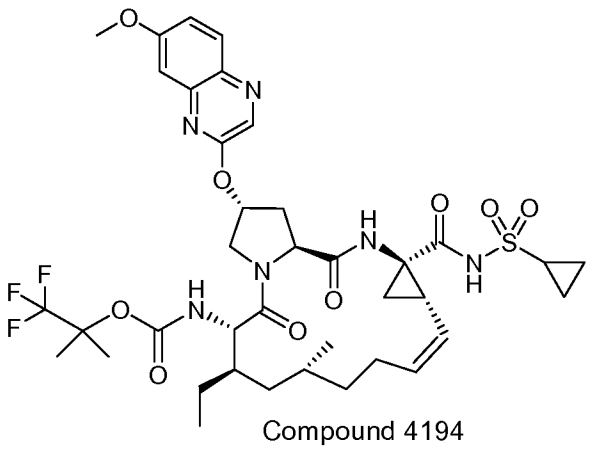


Compound 4193

Compound 4193 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4193: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.96 (d, *J*=5.77 Hz, 1 H) 7.78 (d, *J*=11.80 Hz, 1 H) 7.40 (d, *J*=8.28 Hz, 1 H) 7.31 (d, *J*=6.02 Hz, 1 H) 5.89 (br. s., 1 H) 5.61 (s, 1 H) 4.73 (d, *J*=12.55 Hz, 2 H) 4.64 (br. s., 2 H) 3.99 - 4.09 (m, 6 H) 2.72 (br. s., 2 H) 2.44 (d, *J*=11.80 Hz, 2 H) 1.97 (br. s., 2 H) 1.72 (br. s., 1 H) 1.59 (br. s., 5 H) 1.49 (br. s., 2 H) 1.38 - 1.44 (m, 3 H) 1.25 - 1.35 (m, 6 H) 1.11 (s, 3 H) 1.02 (d, *J*=6.78 Hz, 2 H) 0.92 (s, 1 H) 0.84 (t, *J*=7.53 Hz, 3 H) ; MS: MS *m/z* 872.4 (M^++1).

Preparation of Compound 4194

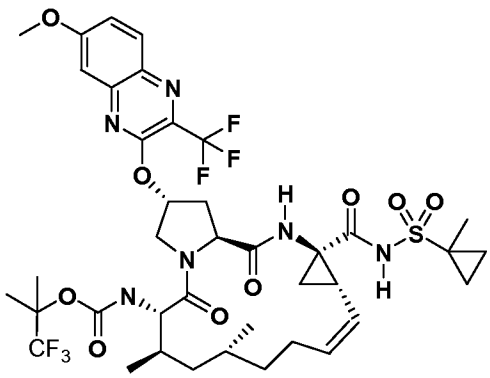


Compound 4194

Compound 4194 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4194: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-7-ethyl-2-(7-methoxyquinoxalin-2-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.06 (s, 1 H) 8.27 (s, 1 H) 7.87 (d, *J*=9.03 Hz, 1 H) 7.32 - 7.38 (m, 1 H) 7.29 (dd, *J*=9.03, 2.76 Hz, 1 H) 5.91 (br. s., 1 H) 5.59 - 5.69 (m, 1 H) 5.05 (t, *J*=9.91 Hz, 1 H) 4.74 (d, *J*=12.30 Hz, 1 H) 4.61 (d, *J*=2.01 Hz, 1 H) 4.03 - 4.10 (m, 2 H) 3.99 (s, 3 H) 3.38 (br. s., 1 H) 2.91 - 2.99 (m, 1 H) 2.66 - 2.75 (m, 2 H) 2.35 - 2.53 (m, 2 H) 1.92 - 2.06 (m, 2 H) 1.80 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.43 - 1.65 (m, 7 H) 1.30 - 1.39 (m, 4 H) 1.20 - 1.26 (m, 4 H) 1.05 - 1.20 (m, 4 H) 1.03 (d, *J*=6.53 Hz, 3 H) 0.82 (t, *J*=7.53 Hz, 3 H) ; MS: MS *m/z* 823.5 (M^++1).

Preparation of Compound 4195

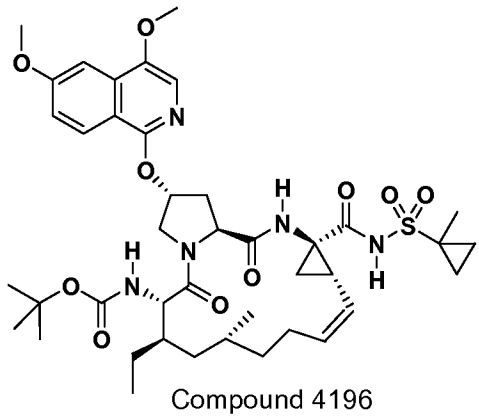


Compound 4195

Compound 4195 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4195: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-methoxy-3-(trifluoromethyl)quinoxalin-2-yloxy)-7,9-dimethyl-14a-(1- methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.98 (br. s., 1 H) 5.62 (br. s., 1 H) 4.98 - 5.06 (m, 1 H) 4.82 (d, *J*=6.02 Hz, 1 H) 4.65 (dd, *J*=10.16, 7.15 Hz, 1 H) 4.02 - 4.08 (m, 4 H) 3.74 (d, *J*=10.79 Hz, 1 H) 2.68 - 2.77 (m, 2 H) 2.40 - 2.54 (m, 2 H) 1.74 - 2.02 (m, 4 H) 1.66 (br. s., 1 H) 1.59 (dd, *J*=9.41, 5.90 Hz, 1 H) 1.53 (s, 3 H) 1.40 - 1.50 (m, 3 H) 1.34 (t, *J*=7.28 Hz, 9 H) 1.21 (s, 3 H) 0.99 (dd, *J*=19.83, 6.53 Hz, 6 H) 0.80 - 0.91 (m, 1 H). MS: MS *m/z* 891.5 (M^++1).

Preparation of Compound 4196

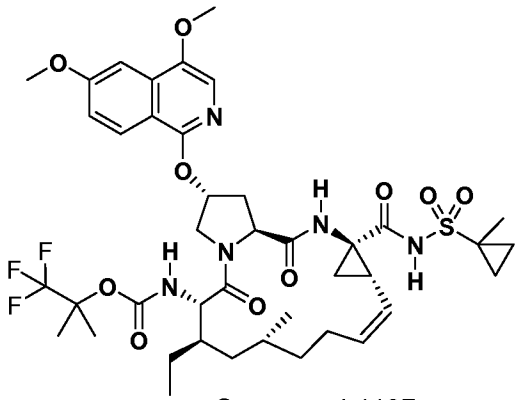


Compound 4196

Compound 4196 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4196: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4,6-dimethoxyisoquinolin-1-yloxy)-7-ethyl-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.06 (d, *J*=9.03 Hz, 1 H) 7.52 (s, 1 H) 7.42 (d, *J*=2.51 Hz, 1 H) 7.12 (dd, *J*=9.03, 2.26 Hz, 1 H) 6.61 (d, *J*=9.54 Hz, 1 H) 5.82 (br. s., 1 H) 5.62 (d, *J*=6.27 Hz, 1 H) 5.02 (d, *J*=10.04 Hz, 1 H) 4.73 (d, *J*=11.04 Hz, 1 H) 4.55 - 4.65 (m, 1 H) 4.07 - 4.17 (m, 1 H) 3.99 - 4.07 (m, 4 H) 3.94 (s, 3 H) 3.24 - 3.31 (m, 2 H) 2.74 (d, *J*=8.03 Hz, 2 H) 2.43 (d, *J*=9.29 Hz, 2 H) 1.95 (br. s., 2 H) 1.77 (br. s., 1 H) 1.49 - 1.69 (m, 6 H) 1.39 - 1.47 (m, 2 H) 1.31 (s, 2 H) 1.15 (s, 9 H) 1.08 (br. s., 2 H) 1.01 (d, *J*=6.78 Hz, 2 H) 0.89 (br. s., 3 H) 0.85 (t, *J*=7.28 Hz, 3 H) ; MS: MS *m/z* 810.4 (M^+-1).

Preparation of Compound 4197

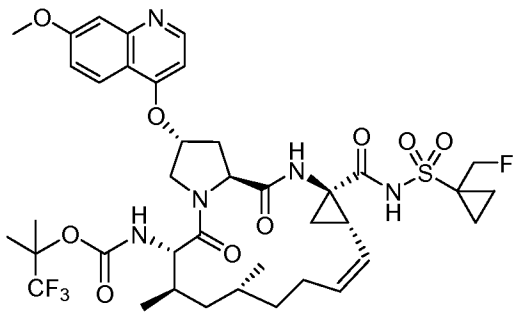


Compound 4197

Compound 4197 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4197: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4,6-dimethoxyisoquinolin-1-yloxy)-7-ethyl-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.05 (d, *J*=9.03 Hz, 1 H) 7.54 (s, 1 H) 7.43 (d, *J*=2.51 Hz, 1 H) 7.28 (d, *J*=8.78 Hz, 1 H) 7.14 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.82 (br. s., 1 H) 5.58 - 5.67 (m, 1 H) 5.01 (t, *J*=10.29 Hz, 1 H) 4.74 (d, *J*=10.54 Hz, 1 H) 4.64 (dd, *J*=10.04, 7.03 Hz, 1 H) 3.98 - 4.13 (m, 5 H) 3.90 - 3.97 (m, 3 H) 2.67 - 2.79 (m, 2 H) 2.42 (ddd, *J*=13.93, 10.16, 4.27 Hz, 2 H) 1.97 (d, *J*=12.55 Hz, 2 H) 1.77 (dd, *J*=8.28, 5.52 Hz, 1 H) 1.66 (d, *J*=9.29 Hz, 1 H) 1.50 - 1.62 (m, 6 H) 1.36 - 1.49 (m, 3 H) 1.31 (s, 2 H) 1.07 - 1.28 (m, 3 H) 0.98 - 1.04 (m, 6 H) 0.87 - 0.95 (m, 3 H) 0.83 (t, *J*=7.53 Hz, 3 H) ; MS: MS *m/z* 864.4 (M^+-1).

Preparation of Compound 4198

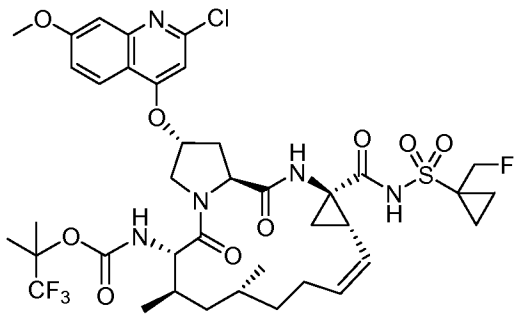


Compound 4198

Compound 4198 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4198: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(7-methoxyquinolin-4-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.65 (d, *J*=5.52 Hz, 1 H) 8.11 (d, *J*=9.03 Hz, 1 H) 7.32 (d, *J*=2.51 Hz, 1 H) 7.14 (dd, *J*=9.29, 2.51 Hz, 1 H) 6.97 (d, *J*=5.52 Hz, 1 H) 5.56 - 5.65 (m, 1 H) 5.52 (br. s., 1 H) 5.09 (br. s., 1 H) 4.78 (d, *J*=11.29 Hz, 2 H) 4.62 (dd, *J*=10.16, 6.90 Hz, 2 H) 4.06 (dd, *J*=11.54, 3.01 Hz, 1 H) 3.94 - 3.97 (m, 3 H) 3.84 (d, *J*=10.79 Hz, 1 H) 2.64 - 2.81 (m, 2 H) 2.33 - 2.56 (m, 2 H) 1.78 - 2.02 (m, 3 H) 1.42 - 1.75 (m, 7 H) 1.38 (s, 3 H) 1.16 - 1.32 (m, 3 H) 0.97 - 1.04 (m, 8 H) 0.84 (t, *J*=11.54 Hz, 1 H). MS: MS *m/z* 840.4 (M^++1).

Preparation of Compound 4199

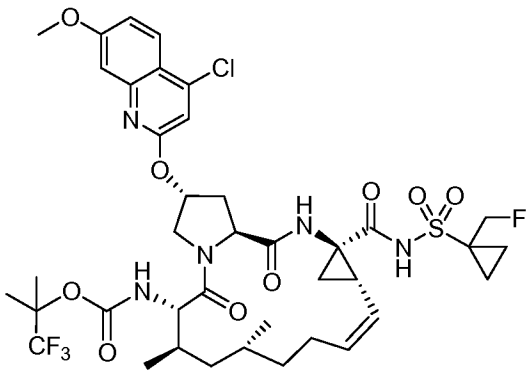


Compound 4199

Compound 4199 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4199: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(2-chloro-7-methoxyquinolin-4-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.06 (d, *J*=9.29 Hz, 1 H) 7.24 (d, *J*=2.26 Hz, 1 H) 7.14 (dd, *J*=9.29, 2.51 Hz, 1 H) 7.02 (s, 1 H) 5.60 (br. s., 1 H) 5.51 (br. s., 1 H) 4.77 - 4.81 (m, 2 H) 4.57 - 4.64 (m, 2 H) 4.03 (dd, *J*=11.80, 3.01 Hz, 1 H) 3.96 (s, 3 H) 3.83 (d, *J*=10.79 Hz, 1 H) 3.23 (d, *J*=7.28 Hz, 2 H) 2.67 - 2.80 (m, 2 H) 2.34 - 2.54 (m, 3 H) 1.93 - 2.03 (m, 1 H) 1.72 (dd, *J*=8.53, 5.52 Hz, 3 H) 1.46 - 1.58 (m, 2 H) 1.38 (s, 3 H) 1.33 (t, *J*=7.28 Hz, 4 H) 0.99 - 1.04 (m, 9 H) 0.80 - 0.88 (m, 1 H). MS: MS *m/z* 874.4 (M^++1).

Preparation of Compound 4200

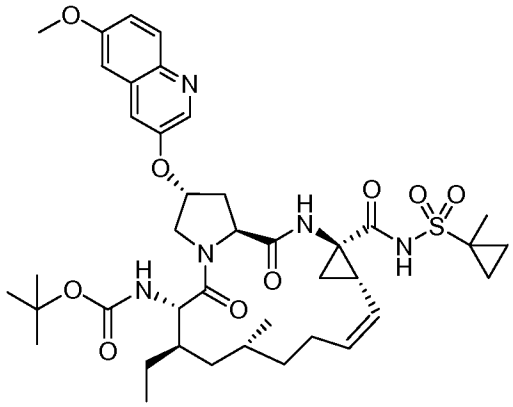


Compound 4200

Compound 4200 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4200: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-chloro-7-methoxyquinolin-2-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.01 (d, *J*=9.04 Hz, 1 H) 7.33 (d, *J*=2.26 Hz, 1 H) 7.17 (dd, *J*=9.16, 2.38 Hz, 1 H) 6.91 (s, 1 H) 5.89 (br. s., 1 H) 5.60 (br. s., 1 H) 4.78 (d, *J*=11.04 Hz, 1 H) 4.68 (d, *J*=11.29 Hz, 1 H) 4.52 - 4.60 (m, 2 H) 4.06 (dd, *J*=11.54, 3.26 Hz, 1 H) 3.97 (s, 3 H) 3.83 (d, *J*=10.79 Hz, 1 H) 2.64 (dd, *J*=13.43, 7.15 Hz, 2 H) 2.36 - 2.51 (m, 2 H) 1.85 - 2.05 (m, 2 H) 1.65 - 1.81 (m, 4 H) 1.42 - 1.62 (m, 4 H) 1.31 - 1.36 (m, 6 H) 1.26 (s, 3 H) 0.95 - 1.04 (m, 6 H) 0.78 - 0.85 (m, 1 H). MS: MS *m/z* 875.34 (M^++1).

Preparation of Compound 4201

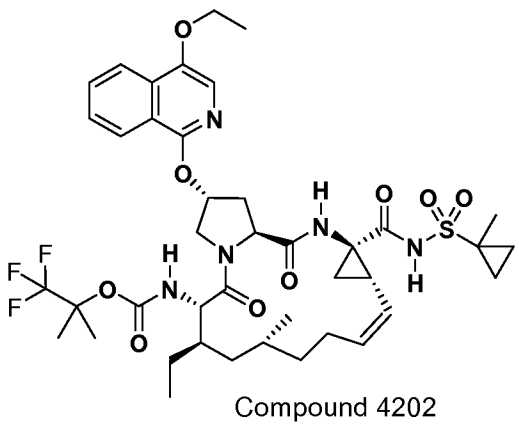


Compound 4201

Compound 4201 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4201: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(6-methoxyquinolin-3-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. MS: MS *m/z* 782.9 (M^++1).

Preparation of Compound 4202

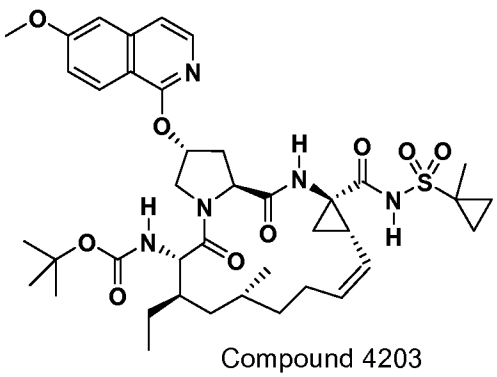


Compound 4202

Compound 4202 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4202: ,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxyisoquinolin-1-yloxy)-7-ethyl-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.15 (dd, *J*=8.91, 2.38 Hz, 2 H) 7.70 - 7.76 (m, 1 H) 7.53 - 7.60 (m, 2 H) 5.84 (br. s., 1 H) 5.57 - 5.67 (m, 1 H) 5.01 (t, *J*=10.04 Hz, 1 H) 4.78 (d, *J*=11.54 Hz, 1 H) 4.66 (dd, *J*=10.29, 7.03 Hz, 1 H) 4.25 (q, *J*=7.03 Hz, 2 H) 3.98 - 4.09 (m, 2 H) 2.67 - 2.79 (m, 2 H) 2.38 - 2.49 (m, 2 H) 1.93 - 2.05 (m, 2 H) 1.72 - 1.79 (m, 1 H) 1.65 (br. s., 1 H) 1.50 - 1.61 (m, 11 H) 1.41 (br. s., 2 H) 1.36 (s, 3 H) 1.31 (s, 2 H) 1.14 (d, *J*=11.80 Hz, 1 H) 1.01 (d, *J*=6.78 Hz, 3 H) 0.92 (s, 3 H) 0.89 (br. s., 2 H) 0.83 (t, *J*=7.40 Hz, 3 H) ; MS: MS *m/z* 850.6 (M^++1).

Preparation of Compound 4203



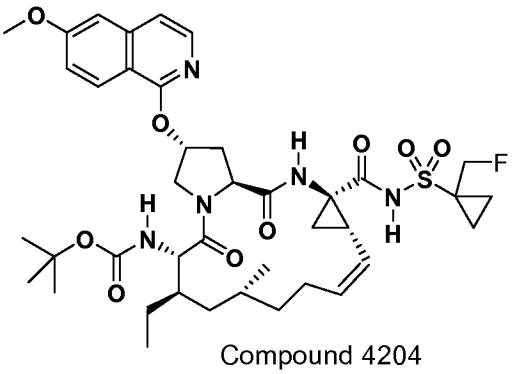
Compound 4203

Compound 4203 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4203: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(6-methoxyisoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.02 (s, 1 H) 8.10 (d, *J*=9.03 Hz, 1 H) 7.92 (d, *J*=6.02 Hz, 1 H) 7.26 (d, *J*=6.02 Hz, 1

H) 7.20 (d, *J*=2.26 Hz, 1 H) 7.09 (dd, *J*=8.91, 2.38 Hz, 1 H) 5.90 (br. s., 1 H) 5.62 (td, *J*=10.04, 6.02 Hz, 1 H) 5.01 (t, *J*=9.91 Hz, 1 H) 4.76 (d, *J*=11.04 Hz, 1 H) 4.62 (dd, *J*=9.91, 7.40 Hz, 1 H) 4.11 (d, *J*=11.29 Hz, 1 H) 4.05 (dd, *J*=11.17, 3.39 Hz, 1 H) 3.94 (s, 3 H) 2.68 - 2.80 (m, 2 H) 2.36 - 2.49 (m, 2 H) 1.89 - 2.05 (m, 2 H) 1.76 (dd, *J*=8.16, 5.65 Hz, 1 H) 1.56 - 1.69 (m, 4 H) 1.52 (s, 4 H) 1.43 (dd, *J*=9.79, 4.52 Hz, 2 H) 1.22 - 1.36 (m, 3 H) 1.13 - 1.19 (m, 9 H) 1.09 (d, *J*=11.04 Hz, 1 H) 1.01 (d, *J*=6.78 Hz, 3 H) 0.82 - 0.93 (m, 5 H) ; MS: MS *m/z* 782.2 (M^++1).

Preparation of Compound 4204

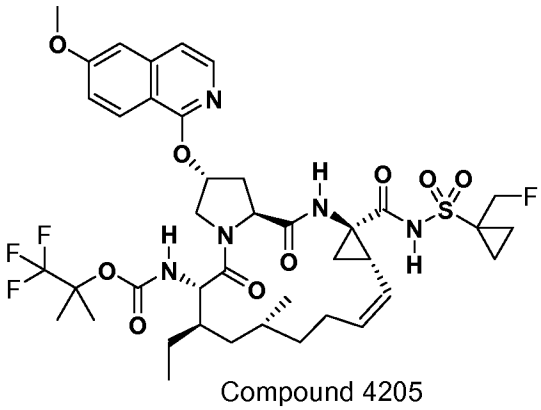


Compound 4204

Compound 4204 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4204: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.10 (d, *J*=9.03 Hz, 1 H) 7.92 (d, *J*=6.02 Hz, 1 H) 7.26 (d, *J*=5.77 Hz, 1 H) 7.20 (d, *J*=2.26 Hz, 1 H) 7.09 (dd, *J*=9.29, 2.26 Hz, 1 H) 6.61 (d, *J*=10.04 Hz, 1 H) 5.89 (br. s., 1 H) 5.62 (d, *J*=5.52 Hz, 1 H) 5.01 (br. s., 1 H) 4.77 (t, *J*=12.17 Hz, 1 H) 4.47 - 4.66 (m, 2 H) 4.02 - 4.14 (m, 2 H) 3.94 (s, 3 H) 2.64 - 2.76 (m, 2 H) 2.43 (d, *J*=10.29 Hz, 2 H) 1.95 (br. s., 2 H) 1.52 - 1.76 (m, 7 H) 1.39 - 1.51 (m, 2 H) 1.31 (s, 4 H) 1.17 (s, 7 H) 1.13 (br. s., 2 H) 1.02 (d, *J*=6.78 Hz, 3 H) 0.85 (t, *J*=7.28 Hz, 3 H) ; MS: MS *m/z* 799.9 (M^+-1).

Preparation of Compound 4205

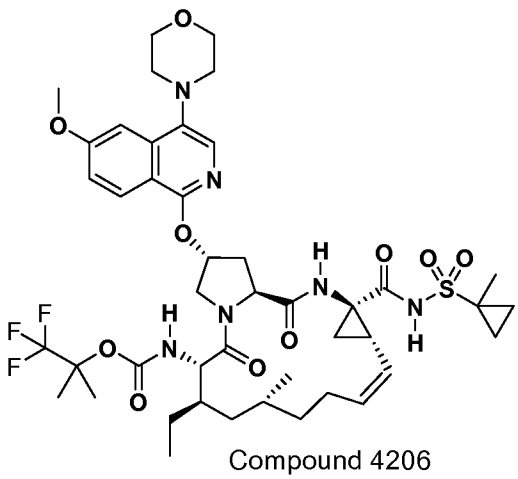


Compound 4205

Compound 4205 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4205: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(6-methoxyisoquinolin-1-yloxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.06 (d, *J*=9.03 Hz, 1 H) 7.91 (d, *J*=6.02 Hz, 1 H) 7.24 (d, *J*=6.02 Hz, 1 H) 7.18 (d, *J*=2.51 Hz, 1 H) 7.08 (dd, *J*=9.29, 2.51 Hz, 1 H) 5.86 (br. s., 1 H) 5.59 (td, *J*=10.16, 6.02 Hz, 1 H) 4.97 (t, *J*=10.16 Hz, 1 H) 4.71 - 4.77 (m, 1 H) 4.59 - 4.63 (m, 1 H) 3.96 - 4.08 (m, 2 H) 3.91 (s, 3 H) 2.68 (dt, *J*=18.07, 9.03 Hz, 2 H) 2.35 - 2.46 (m, 2 H) 1.88 - 2.01 (m, 2 H) 1.61 - 1.72 (m, 3 H) 1.54 (dd, *J*=9.79, 5.77 Hz, 4 H) 1.47 (br. s., 2 H) 1.36 (s, 3 H) 1.07 - 1.29 (m, 5 H) 0.96 - 1.01 (m, 6 H) 0.80 (t, *J*=7.40 Hz, 3 H) ; MS: MS *m/z* 855.6 (M^++1).

Preparation of Compound 4206

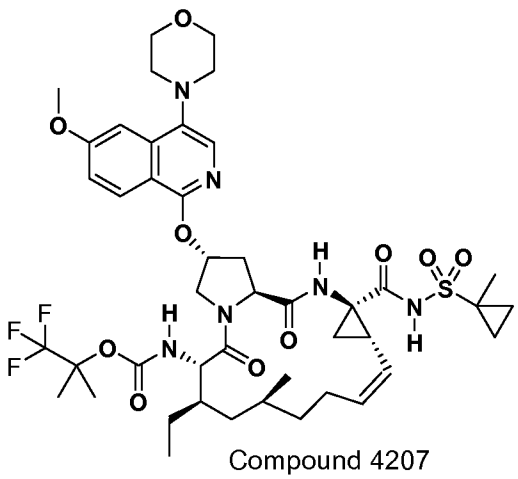


Compound 4206

Compound 4206 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4206: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(6-methoxy-4-morpholinoisoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.10 (d, *J*=9.03 Hz, 1 H) 7.72 (s, 1 H) 7.46 (d, *J*=2.51 Hz, 1 H) 7.14 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.84 (br. s., 1 H) 5.61 (br. s., 1 H) 5.01 (br. s., 1 H) 4.75 (d, *J*=11.54 Hz, 2 H) 4.61 - 4.68 (m, 1 H) 3.99 - 4.08 (m, 2 H) 3.94 - 3.98 (m, 8 H) 3.05 - 3.12 (m, 4 H) 2.73 (dd, *J*=13.80, 6.78 Hz, 2 H) 2.38 - 2.48 (m, 2 H) 1.91 - 2.03 (m, 2 H) 1.77 (dd, *J*=8.41, 5.40 Hz, 1 H) 1.55 - 1.63 (m, 4 H) 1.50 - 1.53 (m, 4 H) 1.39 - 1.47 (m, 2 H) 1.37 (s, 3 H) 1.31 (s, 3 H) 1.13 (d, *J*=13.05 Hz, 1 H) 0.97 - 1.03 (m, 6 H) 0.87 - 0.94 (m, 2 H) 0.83 (t, *J*=7.40 Hz, 3 H) ; MS: MS *m/z* 919.9 (M^+-1).

Preparation of Compound 4207

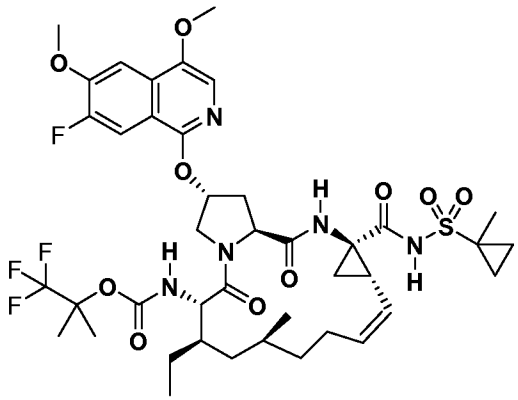


Compound 4207

Compound 4207 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4207: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-(6-methoxy-4-morpholinoisoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.13 (d, J=9.29 Hz, 1 H) 7.71 (s, 1 H) 7.46 (d, J=2.51 Hz, 1 H) 7.14 (dd, J=9.16, 2.38 Hz, 1 H) 5.85 (br. s., 1 H) 5.72 (br. s., 1 H) 5.05 (br. s., 1 H) 4.70 (t, J=8.53 Hz, 1 H) 4.51 - 4.58 (m, 1 H) 4.31 (br. s., 1 H) 4.07 (br. s., 1 H) 3.93 - 3.99 (m, 7 H) 3.66 (d, *J*=2.26 Hz, 1 H) 3.06 - 3.11 (m, 4 H) 2.66 - 2.74 (m, 1 H) 2.46 (br. s., 2 H) 2.21 (t, *J*=7.53 Hz, 1 H) 1.94 - 2.08 (m, 2 H) 1.85 - 1.93 (m, 3 H) 1.72 (br. s., 1 H) 1.60 (d, *J*=7.28 Hz, 3 H) 1.48 - 1.53 (m, 5 H) 1.45 (s, 4 H) 1.28 - 1.37 (m, 8 H) 1.18 (s, 3 H) 0.98 (t, *J*=7.28 Hz, 3 H) 0.92 (d, *J*=6.78 Hz, 3 H) ; MS: MS *m/z* 919.9 (M^{+}-1).

Example 4208: Preparation of Compound 4208

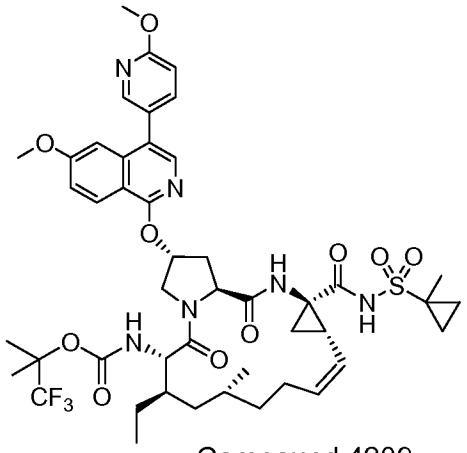


Compound 4208

Compound 4208 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4208: *1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.* ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.78 (d, *J*=11.54 Hz, 1 H) 7.51 - 7.60 (m, 2 H) 5.82 (br. s., 1 H) 5.72 (d, *J*=8.28 Hz, 1 H) 5.13 (br. s., 1 H) 4.66 - 4.72 (m, 1 H) 4.52 (d, *J*=11.04 Hz, 1 H) 4.33 (d, *J*=6.27 Hz, 1 H) 3.99 - 4.09 (m, 8 H) 2.71 (dd, *J*=13.30, 7.28 Hz, 1 H) 2.54 (br. s., 1 H) 2.38 - 2.49 (m, 2 H) 1.94 - 2.06 (m, 2 H) 1.82 - 1.91 (m, 1 H) 1.69 - 1.76 (m, 1 H) 1.60 (br. s., 5 H) 1.50 (d, *J*=9.03 Hz, 6 H) 1.43 (d, *J*=11.04 Hz, 2 H) 1.33 (d, *J*=13.05 Hz, 3 H) 1.27 (s, 2 H) 1.01 (t, *J*=7.40 Hz, 2 H) 0.93 (d, *J*=6.78 Hz, 3 H) 0.85 (br. s., 2 H) ; MS: MS *m/z* 882.4 (M^+-1).

Preparation of Compound 4209

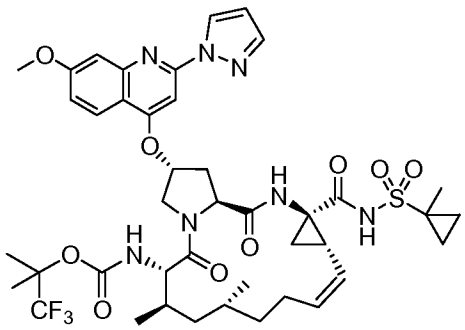


Compound 4209

Compound 4209 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4209: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(6-methoxy-4-(6-methoxypyridin-3-yl)isoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.19 - 8.25 (m, 2 H) 7.90 (s, 1 H) 7.83 (dd, *J*=8.53, 2.51 Hz, 1 H) 7.19 (dd, *J*=9.29, 2.51 Hz, 1 H) 6.97 - 7.06 (m, 2 H) 5.94 (br. s., 1 H) 5.53 - 5.69 (m, 1 H) 4.67 - 4.74 (m, 1 H) 4.00 - 4.11 (m, 5 H) 3.79 - 3.85 (m, 3 H) 2.77 (d, *J*=8.28 Hz, 2 H) 2.40 - 2.55 (m, 2 H) 1.93 - 2.07 (m, 2 H) 1.78 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.51 - 1.62 (m, 8 H) 1.39 (s, 3 H) 1.26 - 1.34 (m, 4 H) 1.06 - 1.19 (m, 2 H) 0.97 - 1.04 (m, 6 H) 0.79 - 0.92 (m, 6 H). MS: MS *m/z* 944.04 (M^++1).

Preparation of Compound 4210

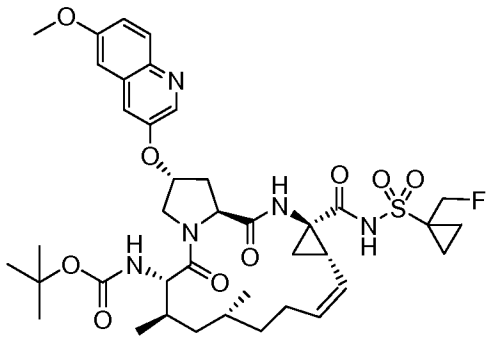


Compound 4210

Compound 4210 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4210: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-methoxy-2-(1H-pyrazol-1-yl)quinolin-4-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.08 (s, 1 H) 8.82 (d, *J*=2.26 Hz, 1 H) 8.09 (d, *J*=9.29 Hz, 1 H) 7.89 (d, *J*=1.26 Hz, 1 H) 7.57 (s, 1 H) 7.38 (d, *J*=2.26 Hz, 1 H) 7.10 (dd, *J*=9.16, 2.38 Hz, 1 H) 6.62 - 6.67 (m, 1 H) 5.59 - 5.68 (m, 2 H) 5.03 (t, *J*=9.91 Hz, 1 H) 4.66 (dd, *J*=10.16, 7.15 Hz, 1 H) 4.11 (dd, *J*=11.67, 2.89 Hz, 1 H) 3.98 (s, 3 H) 3.85 (d, *J*=10.79 Hz, 1 H) 2.85 (dd, *J*=14.05, 7.03 Hz, 1 H) 2.65 - 2.76 (m, 1 H) 2.40 - 2.59 (m, 2 H) 1.76 - 2.03 (m, 4 H) 1.64 - 1.70 (m, 1 H) 1.51 - 1.60 (m, 5 H) 1.41 - 1.48 (m, 2 H) 1.36 (s, 3 H) 1.09 (s, 3 H) 1.01 (dd, *J*=9.29, 6.78 Hz, 6 H) 0.83 - 0.94 (m, 3 H). MS: MS *m/z* 888.96 (M^++1).

Preparation of Compound 4211

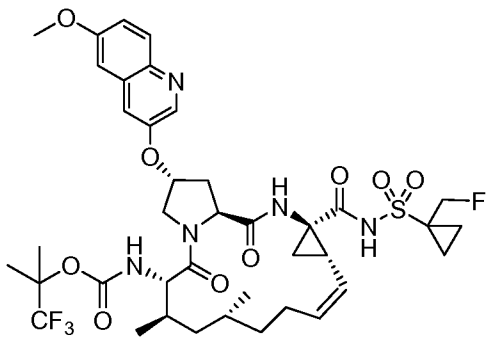


Compound 4211

Compound 4211 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4211: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(6-methoxyquinolin-3-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.36 (d, *J*=2.76 Hz, 1 H) 7.85 (s, 1 H) 7.74 (s, 1 H) 7.24 - 7.31 (m, 2 H) 5.60 (br. s., 1 H) 5.37 (br. s., 1 H) 4.51 - 4.64 (m, 3 H) 4.05 (d, *J*=10.54 Hz, 1 H) 3.96 (s, 3 H) 3.90 (d, *J*=11.04 Hz, 1 H) 2.67 (d, *J*=8.53 Hz, 2 H) 2.33 - 2.54 (m, 3 H) 1.99 (br. s., 2 H) 1.86 (br. s., 3 H) 1.72 (dd, *J*=8.16, 5.40 Hz, 3 H) 1.41 - 1.60 (m, 6 H) 1.21 - 1.36 (m, 6 H) 1.15 (s, 15 H) 0.96 - 1.06 (m, 8 H). MS: MS *m/z* 887.4 (M^++1).

Preparation of Compound 4212

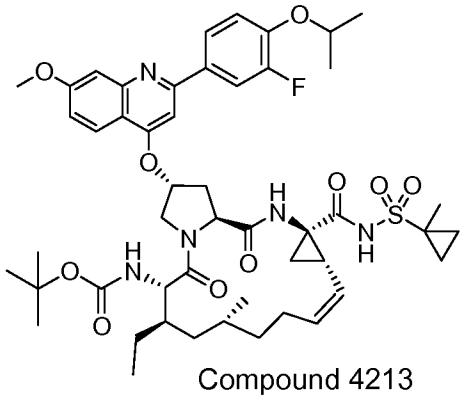


Compound 4212

Compound 4212 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4212: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(6-methoxyquinolin-3-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.49 (d, *J*=2.51 Hz, 1 H) 7.86 - 7.97 (m, 3 H) 7.86 - 7.97 (m, 3 H) 7.32 - 7.39 (m, 3 H) 5.58 - 5.68 (m, 1 H) 5.43 (br. s., 1 H) 5.01 (t, *J*=9.79 Hz, 1 H) 4.49 - 4.71 (m, 3 H) 4.02 - 4.08 (m, 1 H) 3.99 (s, 3 H) 3.85 (d, *J*=10.79 Hz, 1 H) 2.65 - 2.77 (m, 2 H) 2.36 - 2.54 (m, 2 H) 1.86 - 2.03 (m, 3 H) 1.65 - 1.83 (m, 4 H) 1.42 - 1.62 (m, 6 H) 1.16 - 1.36 (m, 10 H) 0.94 - 1.07 (m, 6 H). MS: MS *m/z* 840.89 (M^++1).

Preparation of Compound 4213

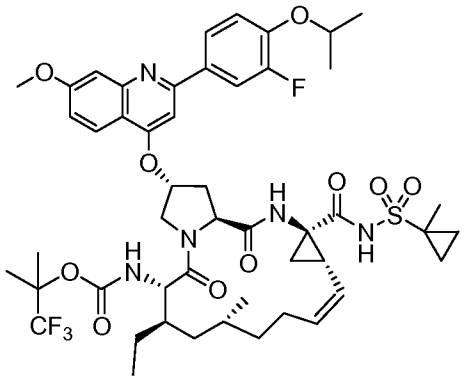


Compound 4213

Compound 4213 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4213: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(2-(3-fluoro-4-isopropoxyphenyl)-7-methoxyquinolin-4-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.07 (d, *J*=9.29 Hz, 1 H) 7.84 - 7.95 (m, 2 H) 7.39 (d, *J*=2.26 Hz, 1 H) 7.25 - 7.31 (m, 2 H) 7.08 (d, *J*=9.03 Hz, 1 H) 6.73 (d, *J*=8.78 Hz, 1 H) 5.63 (br. s., 2 H) 5.03 (br. s., 1 H) 4.75 (dt, *J*=12.11, 6.12 Hz, 1 H) 4.56 - 4.68 (m, 1 H) 4.06 - 4.17 (m, 2 H) 3.97 (s, 3 H) 2.80 (dd, *J*=13.30, 7.03 Hz, 2 H) 2.38 - 2.57 (m, 2 H) 1.98 (br. s., 2 H) 1.73 - 1.83 (m, 1 H) 1.50 - 1.67 (m, 10 H) 1.42 (s, 9 H) 1.31 (br. s., 2 H) 1.17 (s, 10 H) 1.00 - 1.08 (m, 4 H) 0.87 (d, *J*=7.53 Hz, 4 H). MS: MS *m/z* 935.13 (M^++1).

Preparation of Compound 4214

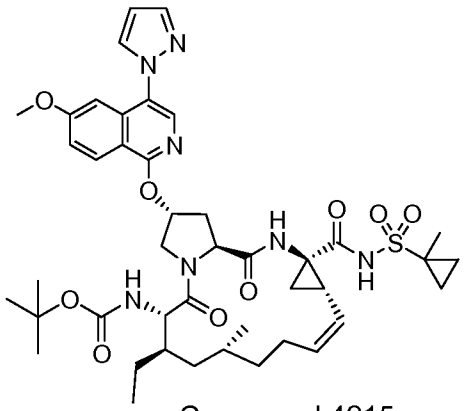


Compound 4214

Compound 4214 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4214: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(2-(3-fluoro-4-isopropoxyphenyl)-7-methoxyquinolin-4-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.06 (d, *J*=9.29 Hz, 1 H) 7.86 - 7.95 (m, 2 H) 7.40 (d, *J*=2.26 Hz, 2 H) 7.24 - 7.32 (m, 2 H) 7.10 (dd, *J*=9.16, 2.38 Hz, 1 H) 5.64 (br. s., 2 H) 5.03 (br. s., 1 H) 4.71 - 4.78 (m, 1 H) 4.66 (d, *J*=17.07 Hz, 1 H) 4.11 (d, *J*=11.29 Hz, 2 H) 3.98 (s, 3 H) 3.66 - 3.80 (m, 2 H) 2.70 - 2.86 (m, 2 H) 2.39 - 2.57 (m, 2 H) 2.01 (br. s., 2 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.49 - 1.64 (m, 9 H) 1.38 - 1.47 (m, 11 H) 1.31 (s, 2 H) 1.16 (d, *J*=11.54 Hz, 1 H) 1.03 (br. s., 4 H) 0.84 - 0.93 (m, 4 H). MS: MS *m/z* 989.09 (M^++1).

Preparation of Compound 4215

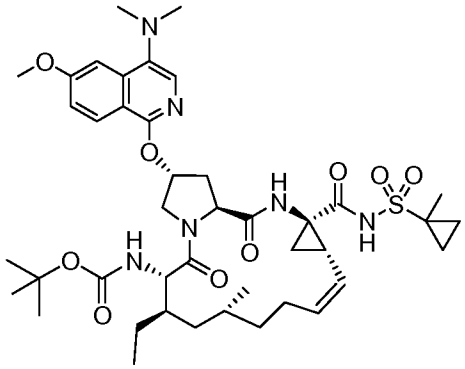


Compound 4215

Compound 4215 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4215: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(6-methoxy-4-(1H-pyrazol-1-yl)isoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.05 (s, 1 H) 8.70 (d, *J*=2.51 Hz, 1 H) 8.09 (d, *J*=9.03 Hz, 1 H) 7.79 (s, 1 H) 7.72 (s, 1 H) 7.23 - 7.31 (m, 1 H) 7.27 (d, *J*=2.26 Hz, 1 H) 7.02 - 7.09 (m, 1 H) 7.02 - 7.10 (m, 1 H) 6.55 - 6.60 (m, 1 H) 6.05 (br. s., 1 H) 5.63 (br. s., 1 H) 4.97 - 5.07 (m, 1 H) 4.64 (dd, *J*=9.66, 7.15 Hz, 1 H) 4.08 - 4.18 (m, 2 H) 3.96 (s, 3 H) 2.70 - 2.86 (m, 2 H) 2.41 - 2.58 (m, 2 H) 1.92 - 2.04 (m, 2 H) 1.77 (dd, *J*=8.28, 5.52 Hz, 1 H) 1.49 - 1.69 (m, 10 H) 1.39 - 1.48 (m, 2 H) 0.95 - 1.07 (m, 7 H) 0.95 - 1.06 (m, 5 H) 0.78 - 0.92 (m, 8 H). MS: MS *m/z* 849.02 (M^++1).

Preparation of Compound 4216

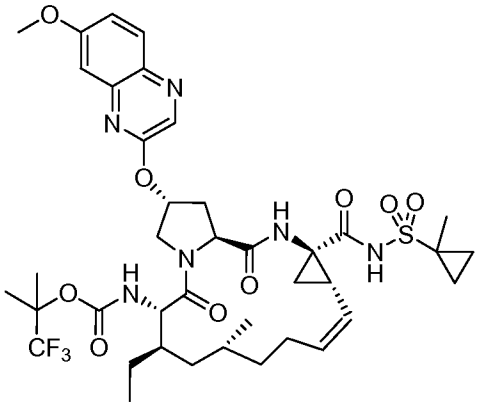


Compound 4216

Compound 4216 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4216: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-(dimethylamino)-6-methoxyisoquinolin-1-yloxy)-7-ethyl-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.10 (d, *J*=9.03 Hz, 1 H) 7.70 (s, 1 H) 7.44 (d, *J*=2.51 Hz, 1 H) 7.41 - 7.47 (m, 1 H) 7.11 (dd, *J*=8.91, 2.38 Hz, 1 H) 6.63 (d, *J*=8.78 Hz, 1 H) 5.84 (br. s., 1 H) 5.62 (d, *J*=5.27 Hz, 1 H) 5.01 (t, *J*=9.79 Hz, 1 H) 4.58 - 4.66 (m, 1 H) 4.01 - 4.16 (m, 2 H) 3.97 (s, 3 H) 2.87 (s, 6 H) 2.68 - 2.79 (m, 2 H) 2.36 - 2.48 (m, 2 H) 1.97 (d, *J*=11.80 Hz, 2 H) 1.77 (dd, *J*=8.03, 5.77 Hz, 1 H) 1.51 - 1.69 (m, 10 H) 1.39 - 1.46 (m, 2 H) 1.22 - 1.35 (m, 3 H) 1.16 (br. s., 9 H) 0.96 - 1.05 (m, 2 H) 0.81 - 0.94 (m, 6 H). MS: MS *m/z* 826.03 (M^++1).

Preparation of Compound 4219

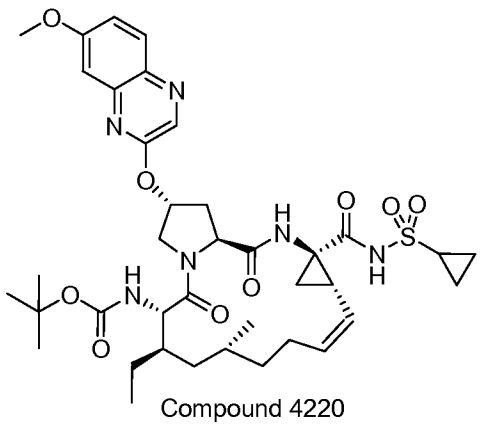


Compound 4219

Compound 4219 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4219: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(7-methoxyquinoxalin-2-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.26 (s, 1 H) 7.87 (d, *J*=9.04 Hz, 1 H) 7.26 - 7.37 (m, 2 H) 5.92 (br. s., 1 H) 5.58 - 5.68 (m, 1 H) 5.02 (t, *J*=10.16 Hz, 2 H) 4.74 (d, *J*=11.29 Hz, 1 H) 4.58 - 4.66 (m, 1 H) 3.97 - 4.12 (m, 5 H) 3.70 - 3.79 (m, 1 H) 2.66 - 2.74 (m, 2 H) 2.37 - 2.54 (m, 2 H) 1.97 (d, *J*=11.80 Hz, 2 H) 1.78 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.49 - 1.61 (m, 9 H) 1.29 - 1.40 (m, 13 H) 1.01 (d, *J*=6.53 Hz, 4 H) 0.87 - 0.94 (m, 5 H). MS: MS *m/z* 837. 2 (M^++1).

Preparation of Compound 4220

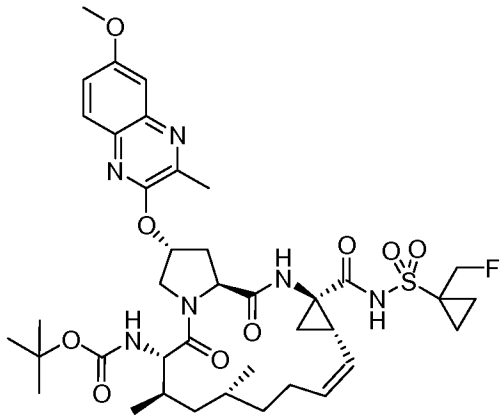


Compound 4220

Compound 4220 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4220: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(6-methoxy-3-methylquinoxalin-2-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.24 (s, 1 H) 7.85 (d, *J*=9.29 Hz, 2 H) 7.82 - 7.88 (m, 1 H) 7.24 - 7.35 (m, 3 H) 7.24 - 7.34 (m, 3 H) 5.92 (br. s., 1 H) 5.61 (d, *J*=5.77 Hz, 1 H) 5.15 (br. s., 1 H) 4.71 (d, *J*=12.30 Hz, 1 H) 4.54 - 4.63 (m, 2 H) 4.03 - 4.11 (m, 3 H) 3.94 - 4.00 (m, 3 H) 2.90 (br. s., 1 H) 2.66 (d, *J*=7.78 Hz, 2 H) 2.35 - 2.56 (m, 2 H) 1.89 - 2.05 (m, 3 H) 1.78 (dd, *J*=8.28, 5.52 Hz, 1 H) 1.40 - 1.62 (m, 6 H) 1.25 - 1.35 (m, 3 H) 1.09 - 1.19 (m, 11 H) 1.02 (d, *J*=6.78 Hz, 4 H) 0.82 (t, *J*=7.28 Hz, 2 H). MS: MS *m/z* 769.52 (M^++1).

Preparation of Compound 4221

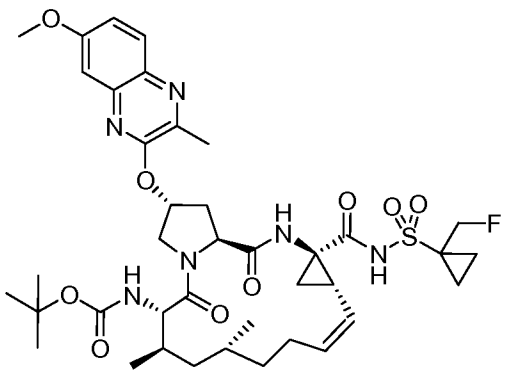


Compound 4221

Compound 4221 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4221: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(6-methoxy-3-methylquinoxalin-2-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.77 (d, *J*=9.04 Hz, 1 H) 7.27 - 7.36 (m, 2 H) 5.89 (br. s., 1 H) 5.56 - 5.66 (m, 1 H) 5.00 (t, *J*=10.16 Hz, 1 H) 4.59 - 4.72 (m, 3 H) 4.05 (dd, *J*=11.80, 3.26 Hz, 1 H) 3.94 (s, 3 H) 3.77 - 3.82 (m, 1 H) 2.69 (dd, *J*=13.30, 7.53 Hz, 2 H) 2.56 (s, 3 H) 2.36 - 2.51 (m, 2 H) 1.92 - 2.01 (m, 1 H) 1.85 (br. s., 2 H) 1.70 - 1.75 (m, 2 H) 1.63 - 1.68 (m, 1 H) 1.55 - 1.60 (m, 1 H) 1.44 - 1.53 (m, 3 H) 1.22 - 1.32 (m, 3 H) 1.18 (s, 9 H) 1.00 (dd, *J*=19.45, 6.65 Hz, 6 H) 0.80 - 0.87 (m, 1 H). MS: MS *m/z* 801.5 (M^++1).

Preparation of Compound 4222

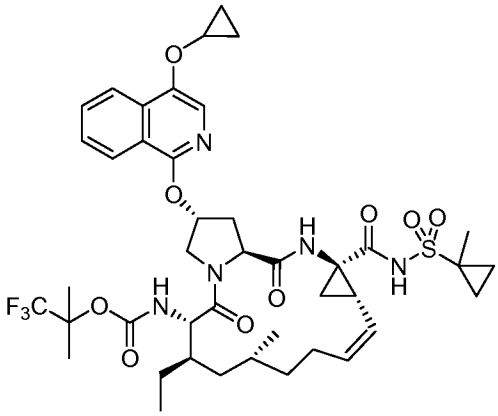


Compound 4222

Compound 4222 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4222: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-2-(7-methoxy-3-methylquinoxalin-2-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.77 (d, *J*=9.04 Hz, 1 H) 7.27 - 7.36 (m, 2 H) 5.89 (br. s., 1 H) 5.56 - 5.66 (m, 1 H) 5.00 (t, *J*=10.16 Hz, 1 H) 4.59 - 4.72 (m, 3 H) 4.05 (dd, *J*=11.80, 3.26 Hz, 1 H) 3.94 (s, 3 H) 3.77 - 3.82 (m, 1 H) 2.69 (dd, *J*=13.30, 7.53 Hz, 2 H) 2.56 (s, 3 H) 2.36 - 2.51 (m, 2 H) 1.92 - 2.01 (m, 1 H) 1.85 (br. s., 2 H) 1.70 - 1.75 (m, 2 H) 1.63 - 1.68 (m, 1 H) 1.55 - 1.60 (m, 1 H) 1.44 - 1.53 (m, 3 H) 1.22 - 1.32 (m, 3 H) 1.18 (s, 9 H) 1.00 (dd, *J*=19.45, 6.65 Hz, 6 H) 0.80 - 0.87 (m, 1 H). MS: MS *m/z* 801.4(M^++1).

Preparation of Compound 4223

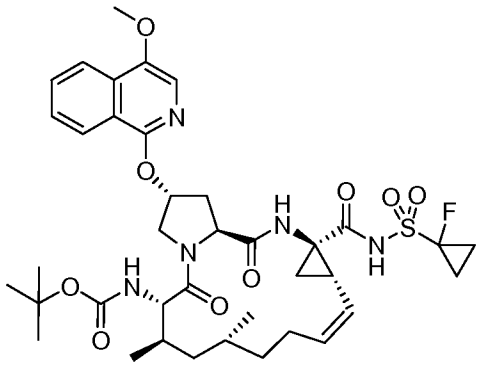


Compound 4223

Compound 4223 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4223: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-cyclopropoxyisoquinolin-1-yloxy)-7-ethyl-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.16 (d, *J*=8.28 Hz, 1 H) 8.04 (d, *J*=8.53 Hz, 1 H) 7.89 - 7.92 (m, 1 H) 7.72 (td, *J*=7.65, 1.00 Hz, 1 H) 7.53 - 7.59 (m, 1 H) 7.29 (d, *J*=8.78 Hz, 1 H) 5.86 (br. s., 1 H) 5.63 (td, *J*=10.10, 5.65 Hz, 1 H) 5.01 (t, *J*=10.16 Hz, 1 H) 4.82 (d, *J*=7.78 Hz, 1 H) 4.68 (dd, *J*=10.16, 7.15 Hz, 1 H) 3.97 - 4.12 (m, 3 H) 2.69 - 2.80 (m, 2 H) 2.38 - 2.49 (m, 2 H) 1.93 - 2.05 (m, 2 H) 1.78 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.64 - 1.70 (m, 1 H) 1.55 - 1.62 (m, 4 H) 1.48 - 1.54 (m, 5 H) 1.40 - 1.47 (m, 2 H) 1.36 (s, 3 H) 1.22 - 1.32 (m, 1 H) 1.14 (t, *J*=12.17 Hz, 1 H) 1.02 (d, *J*=6.78 Hz, 3 H) 0.89 - 0.93 (m, 6 H) 0.81 - 0.87 (m, 5 H). MS: MS *m/z* 860.4 (M^+ -1).

Preparation of Compound 4224

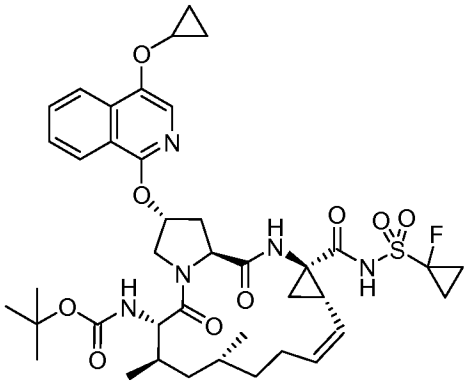


Compound 4224

Compound 4224 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4224: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxy-6-methoxyisoquinolin-1-yloxy)-7-ethyl-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.77 (d, *J*=9.03 Hz, 2 H) 7.29 (d, *J*=2.51 Hz, 2 H) 7.22 (dd, *J*=9.03, 2.76 Hz, 2 H) 5.92 (br. s., 1 H) 5.62 (d, *J*=6.02 Hz, 1 H) 5.01 (br. s., 1 H) 4.72 (d, *J*=11.29 Hz, 1 H) 4.55 - 4.65 (m, 1 H) 4.07 (dd, *J*=11.67, 3.39 Hz, 1 H) 3.96 (s, 3 H) 3.77 - 3.85 (m, 1 H) 2.66 - 2.74 (m, 2 H) 2.50 - 2.57 (m, 4 H) 1.93 - 2.03 (m, 1 H) 1.78 - 1.85 (m, 2 H) 1.73 (dd, *J*=8.53, 5.52 Hz, 2 H) 1.58 (dd, *J*=9.29, 5.52 Hz, 1 H) 1.49 (d, *J*=8.53 Hz, 2 H) 1.22 - 1.32 (m, 3 H) 1.13 - 1.20 (m, 9 H) 1.00 (dd, *J*=18.70, 6.65 Hz, 6 H). MS: MS *m/z* 772.9 (M^++1).

Preparation of Compound 4225

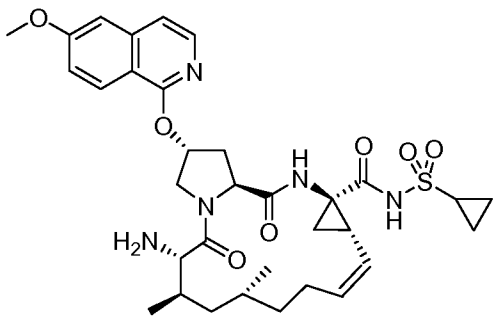


Compound 4225

Compound 4225 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4225: tert-butyl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-cyclopropoxyisoquinolin-1-yloxy)-14a-(1-fluorocyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.16 (d, *J*=8.28 Hz, 1 H) 7.99 - 8.03 (m, 1 H) 7.87 (s, 1 H) 7.70 (t, *J*=7.65 Hz, 1 H) 7.51 - 7.56 (m, 1 H) 5.82 (br. s., 1 H) 5.54 (br. s., 1 H) 4.70 (br. s., 1 H) 4.57 (br. s., 1 H) 4.05 (dd, *J*=11.67, 3.14 Hz, 1 H) 3.98 (tt, *J*=5.99, 2.92 Hz, 1 H) 3.90 (d, *J*=10.79 Hz, 1 H) 3.06 (q, *J*=7.28 Hz, 2 H) 2.72 (d, *J*=7.03 Hz, 2 H) 2.33 - 2.52 (m, 3 H) 1.98 (br. s., 1 H) 1.83 (br. s., 3 H) 1.72 (br. s., 1 H) 1.58 (br. s., 1 H) 1.45 (d, *J*=6.78 Hz, 3 H) 1.32 (t, *J*=7.28 Hz, 3 H) 1.11 (s, 8 H) 0.97 - 1.02 (m, 4 H) 0.87 - 0.92 (m, 3 H) 0.81 - 0.86 (m, 3 H). MS: MS *m/z* 798.7 (M^++1).

Preparation of Compound 4226

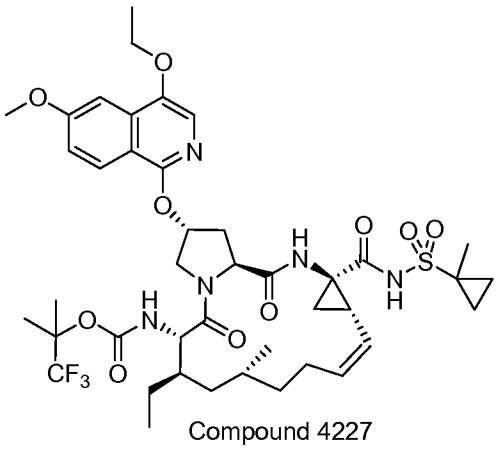


Compound 4226

Compound 4226 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4226: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(cyclopropylsulfonyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 654.3 (M^+-36).

Preparation of Compound 4227

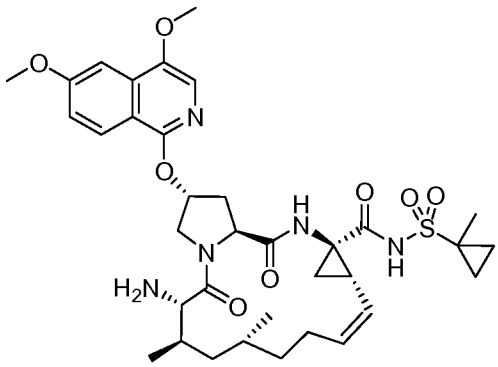


Compound 4227

Compound 4227 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4227: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(4-ethoxy-6-methoxyisoquinolin-1-yloxy)-7-ethyl-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.05 (d, *J*=9.03 Hz, 1 H) 7.53 (s, 1 H) 7.45 (d, *J*=2.51 Hz, 1 H) 7.15 (dd, *J*=9.16, 2.64 Hz, 1 H) 5.82 (br. s., 1 H) 5.63 (d, *J*=5.77 Hz, 1 H) 5.01 (t, *J*=9.66 Hz, 2 H) 4.74 (d, *J*=11.29 Hz, 1 H) 4.65 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.25 (q, *J*=6.86 Hz, 2 H) 3.99 - 4.11 (m, 2 H) 3.96 (s, 3 H) 2.74 (d, *J*=9.79 Hz, 2 H) 2.44 (d, *J*=10.04 Hz, 2 H) 1.94 - 2.04 (m, 2 H) 1.77 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.51 - 1.60 (m, 10 H) 1.37 - 1.44 (m, 5 H) 1.31 (s, 3 H) 1.09 - 1.19 (m, 1 H) 0.98 - 1.04 (m, 6 H) 0.85 - 0.93 (m, 4 H). MS: MS *m/z* 880.4 (M^++1).

Preparation of Compound 4228



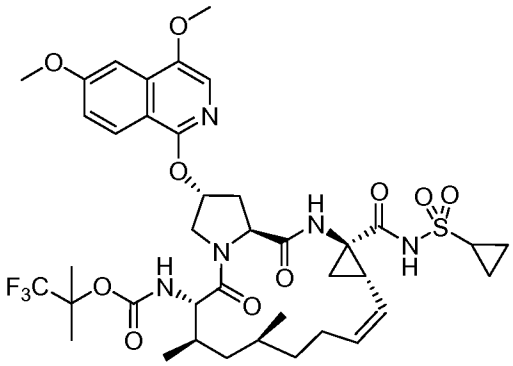
Compound 4228

Compound 4228 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4228: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-2-(4,6-dimethoxyisoquinolin-1-yloxy)-7,9-dimethyl-N-(1-methylcyclopropylsulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide: ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.10 (d, *J*=9.29 Hz, 1 H) 7.53 (s, 1 H) 7.46 (d, *J*=2.26 Hz, 1 H) 7.23 (dd, *J*=9.16, 2.13 Hz, 1 H) 5.90 (br. s., 1 H) 5.60 -

5.69 (m, 1 H) 5.04 (t, *J*=10.04 Hz, 1 H) 4.69 - 4.74 (m, 1 H) 4.22 - 4.28 (m, 1 H) 4.11 - 4.17 (m, 1 H) 4.03 (s, 3 H) 3.96 (s, 3 H) 3.79 (d, *J*=10.29 Hz, 1 H) 2.67 - 2.79 (m, 2 H) 2.49 - 2.59 (m, 2 H) 2.04 (dd, *J*=13.30, 7.78 Hz, 2 H) 1.92 (br. s., 1 H) 1.78 - 1.84 (m, 1 H) 1.66 (d, *J*=10.04 Hz, 1 H) 1.55 - 1.59 (m, 2 H) 1.53 (s, 3 H) 1.32 - 1.50 (m, 4 H) 1.13 (d, *J*=6.27 Hz, 3 H) 1.06 (d, *J*=7.03 Hz, 3 H) 0.97 - 1.02 (m, 1 H) 0.90 (s, 2 H) MS: MS *m/z* 696.2 (M^+-1).

Preparation of Compound 4229



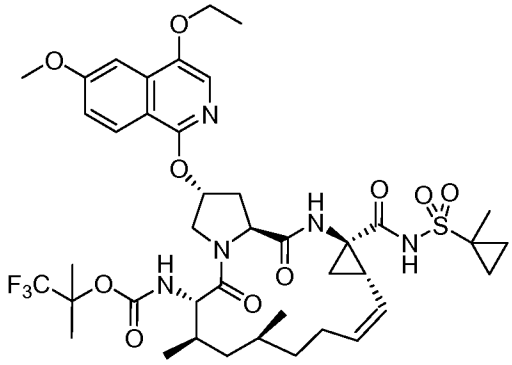
Compound 4229

Compound 4229 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4229: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(4,6-dimethoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate: ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.07 (d, *J*=9.29 Hz, 1 H) 7.53 (s, 1 H) 7.44 (d, *J*=2.51 Hz, 1 H) 7.14 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.81 (br. s., 1 H) 5.58 - 5.67 (m, 1 H) 5.05 (br. s., 1 H) 4.56 - 4.73 (m, 3 H) 4.03 (s, 3 H) 3.95 (s, 3 H) 3.83 (d, *J*=10.79 Hz, 1 H) 2.93 (td, *J*=8.34, 4.14 Hz, 1 H) 2.73 (dd, *J*=13.18, 6.15 Hz, 2 H) 2.37 - 2.47 (m, 2 H) 1.92 - 2.06 (m, 1 H) 1.74 - 1.92 (m, 3 H) 1.59 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.50 (d, *J*=7.03 Hz, 2 H) 1.39 (s, 3 H) 1.21 -

1.33 (m, 3 H) 1.10 (dd, *J*=9.79, 5.27 Hz, 2 H) 1.02 - 1.05 (m, 7 H) 0.99 (d, *J*=6.53 Hz, 3 H) 0.83 (t, *J*=13.68 Hz, 1 H). MS: MS *m/z* 836.2 (M^+-1).

Preparation of Compound 4230

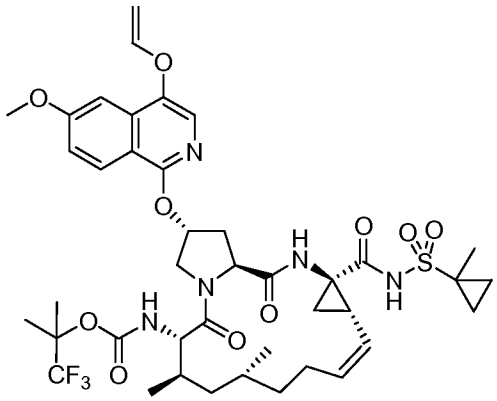


Compound 4230

Compound 4230 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4230: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-(4-ethoxy-6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate: ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.06 (s, 1 H) 8.07 (d, *J*=9.03 Hz, 1 H) 7.52 (s, 1 H) 7.45 (d, *J*=2.26 Hz, 1 H) 7.15 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.81 (br. s., 1 H) 5.63 (td, *J*=10.48, 5.40 Hz, 1 H) 5.01 (t, *J*=9.79 Hz, 1 H) 4.63 - 4.74 (m, 2 H) 4.24 (q, *J*=7.03 Hz, 2 H) 3.99 - 4.06 (m, 1 H) 3.96 (s, 3 H) 3.84 (d, *J*=10.54 Hz, 1 H) 2.67 - 2.77 (m, 2 H) 2.35 - 2.48 (m, 2 H) 1.74 - 2.01 (m, 4 H) 1.63 - 1.70 (m, 1 H) 1.51 - 1.59 (m, 8 H) 1.42 - 1.49 (m, 2 H) 1.39 (s, 3 H) 1.20 - 1.32 (m, 1 H) 0.98 - 1.05 (m, 9 H) 0.81 - 0.92 (m, 3 H). MS: MS *m/z* 864.4 (M^+-1).

Preparation of Compound 4231

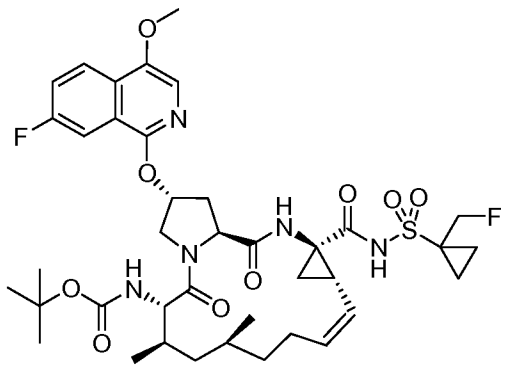


Compound 4231

Compound 4231 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4231: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-N-(cyclopropylsulfonyl)-2-(6-methoxyisoquinolin-1-yloxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. MS: MS *m/z* 864.95 (M^++1).

Preparation of Compound 4232

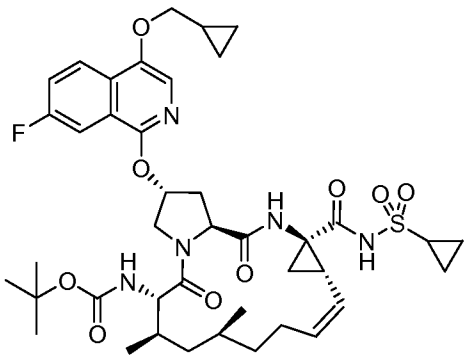


Compound 4232

Compound 4232 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4232: 1tert-butyl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-(7-fluoro-4-methoxyisoquinolin-1-yloxy)-14a-(1-(fluoromethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate: ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17 (dd, *J*=9.16, 5.14 Hz, 1 H) 7.77 (d, *J*=7.53 Hz, 1 H) 7.51 - 7.57 (m, 2 H) 5.84 (br. s., 1 H) 5.60 - 5.72 (m, 1 H) 4.62 - 4.72 (m, 2 H) 4.50 (d, *J*=11.80 Hz, 1 H) 4.17 (d, *J*=7.53 Hz, 1 H) 4.03 (s, 3 H) 2.66 - 2.73 (m, 1 H) 2.49 (br. s., 2 H) 1.99 (br. s., 2 H) 1.62 (br. s., 5 H) 1.36 - 1.50 (m, 5 H) 1.28 - 1.33 (m, 2 H) 1.22 (s, 9 H) 1.11 (d, *J*=6.78 Hz, 7 H) 0.93 (br. s., 3 H). MS: MS *m/z* 803.4 (M^+-1).

Preparation of Compound 4234



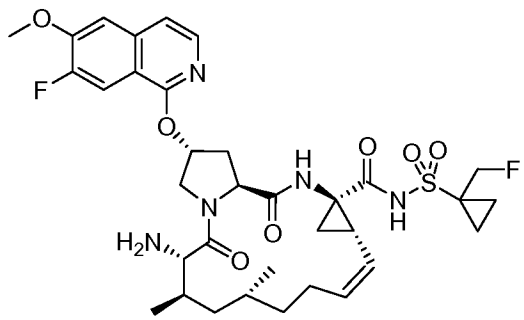
Compound 4234

Compound 4234 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4234: tert-butyl (2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-(4-(cyclopropylmethoxy)-7-fluoroisoquinolin-1-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate: ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.23 (dd, *J*=8.91, 5.40 Hz, 1 H) 7.76 (dd, *J*=9.54, 2.26 Hz, 1 H) 7.52 - 7.58 (m, 2 H) 5.83 (br. s., 1 H) 5.69 (d, *J*=8.78 Hz, 1 H) 5.20 (br. s., 1 H) 4.59 - 4.70 (m, 1 H) 4.51 (d, *J*=11.04 Hz, 1 H) 4.15 (d, *J*=6.78 Hz, 2 H) 4.03 (d, *J*=6.78 Hz, 2 H) 3.24 (s, 1 H) 2.90 (d, *J*=4.77 Hz, 1 H) 2.71 (dd, *J*=13.80, 7.78 Hz, 2 H) 2.41 - 2.53 (m, 2 H) 1.98

(d, *J*=4.52 Hz, 3 H) 1.70 - 1.78 (m, 2 H) 1.65 (br. s., 1 H) 1.29 - 1.45 (m, 7 H) 1.21 (s, 9 H) 1.09 (d, *J*=6.78 Hz, 3 H) 0.93 (d, *J*=7.03 Hz, 3 H) 0.66 - 0.73 (m, 2 H) 0.43 - 0.48 (m, 2 H); MS: MS *m/z* 812.4 (M^++1).

Preparation of Compound 4235

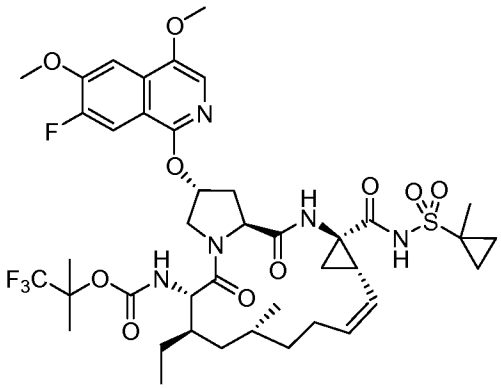


Compound 4235

Compound 4235 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4235: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-2-(7-fluoro-6-methoxyisoquinolin-1-yloxy)-N-(1-(fluoromethyl)cyclopropylsulfonyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide: ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.16 (s, 1 H) 7.95 (d, *J*=5.77 Hz, 1 H) 7.86 (d, *J*=11.54 Hz, 1 H) 7.44 (d, *J*=8.03 Hz, 1 H) 7.35 (d, *J*=6.02 Hz, 1 H) 5.97 (br. s., 1 H) 5.63 (td, *J*=10.29, 5.52 Hz, 1 H) 5.03 (t, *J*=10.16 Hz, 1 H) 4.78 - 4.82 (m, 1 H) 4.71 (dd, *J*=9.41, 7.40 Hz, 1 H) 4.47 - 4.63 (m, 1 H) 4.24 - 4.29 (m, 1 H) 4.13 - 4.17 (m, 1 H) 4.04 (s, 3 H) 3.79 (d, *J*=10.29 Hz, 1 H) 3.66 - 3.71 (m, 3 H) 3.46 - 3.54 (m, 2 H) 2.45 - 2.79 (m, 2 H) 1.98 - 2.13 (m, 2 H) 1.85 - 1.94 (m, 1 H) 1.65 - 1.77 (m, 3 H) 1.53 - 1.61 (m, 2 H) 1.30 - 1.48 (m, 2 H) 1.20 (t, *J*=7.03 Hz, 3 H) 1.13 (d, *J*=6.53 Hz, 3 H) 1.06 (d, *J*=6.78 Hz, 3 H) 0.96 - 1.02 (m, 1 H). MS: MS *m/z* 704.8 (M^++1).

Preparation of Compound 4236

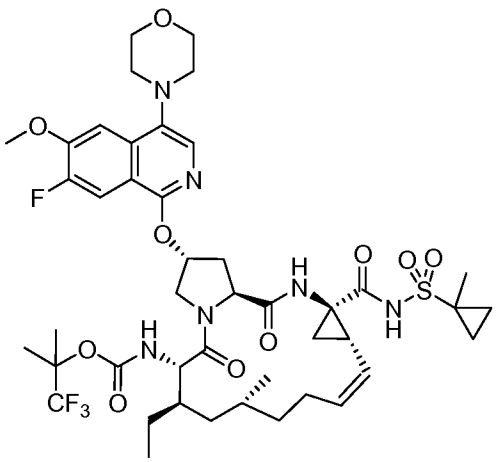


Compound 4236

Compound 4236 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4236: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate: ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.73 (d, *J*=11.54 Hz, 1 H) 7.53 - 7.60 (m, 2 H) 5.82 (br. s., 1 H) 5.62 (td, *J*=10.10, 6.40 Hz, 1 H) 5.01 (t, *J*=9.91 Hz, 1 H) 4.57 - 4.75 (m, 3 H) 3.98 - 4.08 (m, 8 H) 2.67 - 2.77 (m, 2 H) 2.37 - 2.47 (m, 2 H) 1.92 - 2.04 (m, 2 H) 1.73 - 1.79 (m, 1 H) 1.54 - 1.69 (m, 6 H) 1.52 (s, 3 H) 1.44 (d, *J*=3.76 Hz, 2 H) 1.40 (s, 3 H) 1.21 - 1.34 (m, 1 H) 1.12 - 1.17 (m, 1 H) 1.09 (s, 3 H) 1.01 (d, *J*=6.78 Hz, 3 H) 0.87 - 0.93 (m, 2 H) 0.81 - 0.85 (m, 3 H). MS: MS *m/z* 884.5 (M^++1).

Preparation of Compound 4237

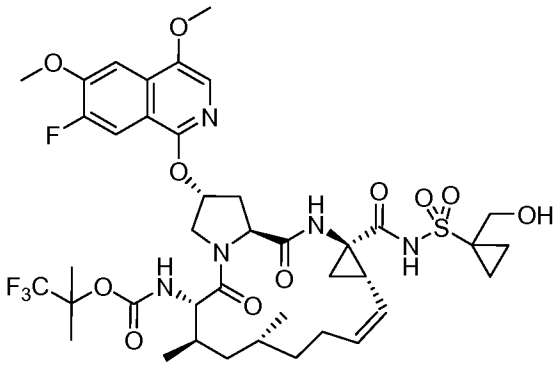


Compound 4237

Compound 4237 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4237: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-(7-methoxyquinoxalin-2-yloxy)-9-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.74 - 7.81 (m, 2 H) 7.60 (d, *J*=8.28 Hz, 1 H) 5.86 (br. s., 1 H) 5.62 (d, *J*=5.27 Hz, 1 H) 5.04 (br. s., 1 H) 4.73 (d, *J*=11.54 Hz, 1 H) 4.64 (dd, *J*=10.16, 7.15 Hz, 1 H) 4.02 - 4.09 (m, 5 H) 3.94 - 4.00 (m, 5 H) 3.06 - 3.12 (m, 4 H) 2.68 - 2.78 (m, 2 H) 2.44 (ddd, *J*=13.80, 10.04, 4.02 Hz, 2 H) 1.94 - 2.04 (m, 3 H) 1.77 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.57 - 1.68 (m, 4 H) 1.53 (s, 4 H) 1.38 - 1.45 (m, 4 H) 1.08 - 1.18 (m, 4 H) 1.02 (d, *J*=6.78 Hz, 3 H) 0.81 - 0.92 (m, 6 H). MS: MS *m/z* 939.4 (M^++1).

Preparation of Compound 4238

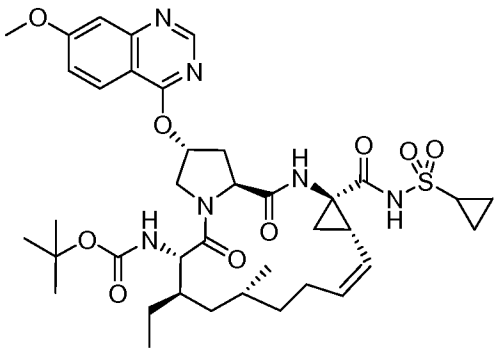


Compound 4238

Compound 4238 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4238: 1,1,1-trifluoro-2-methylpropan-2-yl (2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-(7-fluoro-4,6-dimethoxyisoquinolin-1-yloxy)-14a-(1-(hydroxymethyl)cyclopropylsulfonylcarbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate: ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.78 (s, 1 H) 7.76 (d, *J*=11.54 Hz, 1 H) 7.53 - 7.61 (m, 2 H) 5.80 (br. s., 1 H) 5.58 (td, *J*=10.35, 5.14 Hz, 1 H) 5.34 - 5.43 (m, 1 H) 4.52 - 4.66 (m, 3 H) 4.38 (d, *J*=12.30 Hz, 1 H) 4.04 (d, *J*=0.75 Hz, 6 H) 3.99 (dd, *J*=11.29, 3.51 Hz, 1 H) 3.83 (d, *J*=11.04 Hz, 1 H) 2.57 - 2.72 (m, 2 H) 2.37 - 2.50 (m, 2 H) 1.80 - 1.92 (m, 3 H) 1.66 - 1.74 (m, 2 H) 1.39 - 1.45 (m, 5 H) 1.31 (s, 2 H) 1.19 - 1.28 (m, 2 H) 1.16 (s, 3 H) 1.08 (dd, *J*=9.29, 2.01 Hz, 1 H) 0.98 - 1.04 (m, 6 H) 0.92 (br. s., 1 H) 0.78 (t, *J*=11.67 Hz, 1 H). MS: MS *m/z* 886.96 (M^++1).

Preparation of Compound 4239



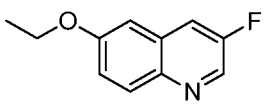
Compound 4239

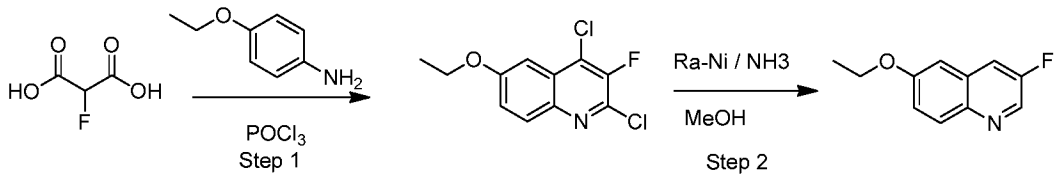
Compound 4239 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 1.

Compound 4239: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-methoxyquinazolin-4-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.73 (s, 1 H) 8.08 (d, *J*=9.29 Hz, 1 H) 7.26 (d, *J*=2.26 Hz, 1 H) 7.20 (dd, *J*=9.03, 2.51 Hz, 1 H) 6.63 (d, *J*=8.28 Hz, 1 H) 6.00 (br. s., 1 H) 5.63 (td, *J*=10.16, 6.53 Hz, 1 H) 5.05 (t, *J*=10.04 Hz, 1 H) 4.64 (dd, *J*=10.04, 7.28 Hz, 1 H) 4.01 - 4.08 (m, 2 H) 3.98 (s, 3 H) 2.89 - 2.97 (m, 1 H) 2.68 - 2.81 (m, 2 H) 2.35 - 2.53 (m, 2 H) 1.90 - 2.03 (m, 2 H) 1.79 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.44 - 1.63 (m, 7 H) 1.24 - 1.38 (m, 3 H) 1.06 - 1.17 (m, 12 H) 1.02 (d, *J*=6.53 Hz, 3 H) 0.83 (t, *J*=7.40 Hz, 3 H). MS: MS *m/z* 769.92 (M^++1).

Scheme: Preparation of 6-ethoxy-3-fluoroquinoline:

6-ethoxy-3-fluoroquinoline





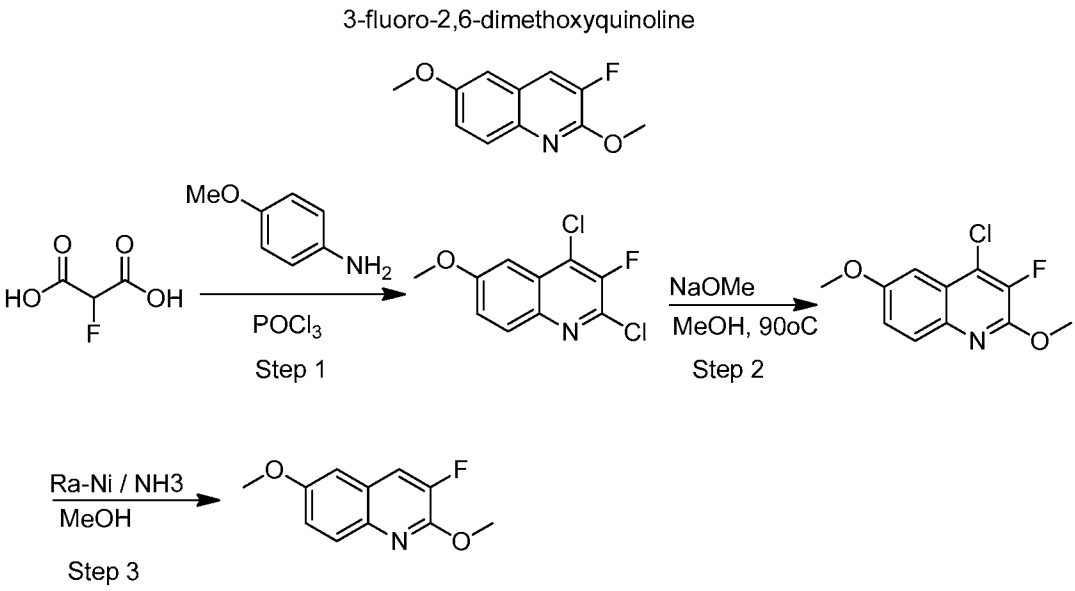
Step: 1 Synthesis of 2,4-dichloro-6-ethoxy-3-fluoroquinoline:

2-Fluoromalonic acid (1 g, 8.199 mmol) was combined with $POCl_3$ (6 ml, 64.4 mmol) and heated to 80 °C to dissolve all of the solids. Once the solids were dissolved, the reaction was cooled to 60 °C; 4-ethoxyaniline (1.124 g, 8.19 mmol) was added portionwise carefully. Once the addition is complete, the reaction mixture was slowly heated to reflux at 100-105 °C for 2h. Removed the volatiles under vacuum, resulting residue was cooled to 0-10 °C; ice was carefully added into the reaction mixture, stirred vigorously to get the solid. NH_4OH is slowly added until the pH was 9.5; stirred the resulting yellow suspension for another 10 min. Filtered the solids, washed with water, then dried the yellow solids to afford 2,4-dichloro-6-ethoxy-3-fluoroquinoline (0.6 g, 2.30 mmol, 28.2 % yield).^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.93-7.90 (d, J = 9.1 Hz, 1H), 7.39--7.36 (dd, J = 9.0 Hz, J= 2.9 Hz, 1H), 7.33-7.32 (d, J= 2.9 Hz 1 H), 4.23-4.18 (m, 2H), 1.53-1.50 (t, 3H), MS: MS *m/z* 260.0 (M^++2).

Step 2: Synthesis of 6-ethoxy-3-fluoroquinoline

To a suspension of 2,4-dichloro-6-ethoxy-3-fluoroquinoline (0.45 g, 1.73 mmol) in ammonia in methanol (5 mL, 10 mmol) was added carefully the slurry of Raney Nickel (0.5 g, 1.73 mmol) in methanol (10 mL). The resulting reaction mixture was hydrogenated at 150 psi pressure, stirred at room temperature for 24 h. Filtered the catalyst, washed with methanol, evaporated the filtrate under reduced pressure to afford crude mass , purified by silica gel chromatography eluting with 10% -50% ethyl acetate in pet-ether to afford 6-ethoxy-3-fluoroquinoline (0.21g, 63%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.64-8.63 (d, J= 2.9Hz, 1H), 7.99-7.97 (d, J = 9 Hz, 1H) 7.65-7.64 (dd, J = 9 Hz, J= 2.9 Hz 1H), 7.33-7.30 (dd, J = 9.0 Hz, J= 2.9 Hz, 1H), 7.03 (d, J= 2.9 Hz 1H), 4.18-4.12 (m, 2H), 1.56-1.47(t, 3H). MS: MS *m/z* 192.1 (M^++1).

Scheme: Preparation of 3-fluoro-2,6-dimethoxyquinoline



Step: 1 Synthesis of 2,4-dichloro-3-fluoro-6-methoxyquinoline:

2-Fluoromalonic acid (2 g, 16.29 mmol) was combined with $POCl_3$ (12 ml, 129 mmol) and heated to 80 °C to dissolve all of the solids. Once the solids were dissolved, the reaction was cooled to 60 °C; 4-methoxyaniline (2.01 g, 16.29 mmol) was added portionwise carefully. Once the addition is complete, the reaction mixture was slowly heated and reflux at 100-105 °C for 2h. Removed the volatiles under vacuum, resulting residue was cooled to 0-10 °C; ice was carefully added into the reaction mixture, stirred vigorously to get the solid. NH_4OH is slowly added until the pH 9.5, stirred the resulting yellow suspension for another 10 min. Filtered the solids , washed with water and then dried the yellow solids to afford 2,4-dichloro-3-fluoro-6-methoxyquinoline (1.20 g, 4.88 mmol, 30 % yield). ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.93 (d, J = 9.1 Hz, 1H), 7.40-7.34 (dd, J = 9.0 Hz, J= 2.9 Hz, 1H), 7.26-7.25 (d, J= 2.9 Hz 1 H), 3.98 (s, 3H), MS: MS *m/z* 247 (M^++2).

Step: 2 Synthesis of 4-chloro-3-fluoro-2,6-dimethoxyquinoline:

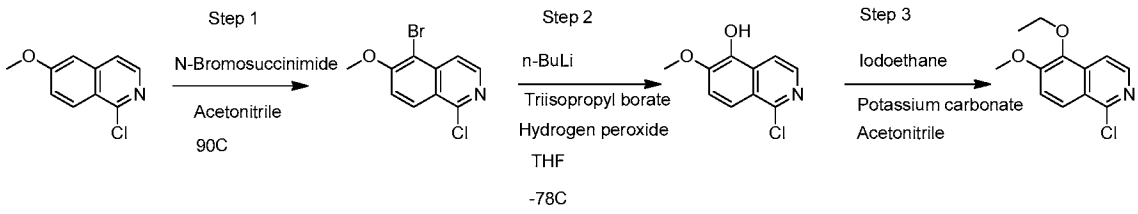
To a suspension of 2,4-dichloro-3-fluoro-6-methoxyquinoline (1 g, 4.06 mmol) in methanol (10 mL) was added sodium methanolate in methanol (0.285 g, 5.28 mmol) , heated to reflux at 90 °C for overnight. Removed the volatiles to half the volume under reduced pressure, quenched the reaction mixture by pouring onto

crushed ice; extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4; filtered; then evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography to afford 4-chloro-3-fluoro-2,6-dimethoxyquinoline (0.52 g, 2.152 mmol, 53.0 % yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.65 (d, J= 2.9Hz, 1H), 8.01-7.98 (d, *J* = 9 Hz, 1H) 7.67-7.64 (dd, *J* = 9 Hz, J= 2.9 Hz 1H), 7.33-7.30 (dd, *J* = 9.0 Hz, J= 2.9 Hz, 1H), 7.03 (d, J= 2.9 Hz 1H), 3.93 (s, 3H). MS: MS *m/z* 242.3 (M^++1).

Step 3: Synthesis of 3-Fluoro-2,6-methoxy quinoline:

To a suspension of 2, 4-dichloro-3-fluoro-6-methoxyquinoline (0.52 g, 2.15 mmol) in ammonia in methanol (10 mL, 462 mmol) was added carefully the slurry of Raney Nickel (0.5 g, 2.15 mmol) in methanol (10 mL). The resulting reaction mixture was hydrogenated at 150 psi pressure, stirred at room temperature for 72 h. Filtered the catalyst, washed with methanol, evaporated the filtrate under reduced pressure to afford crude mass , purified by silica gel chromatography eluting with 10% -50% ethyl acetate in pet-ether to afford 3-Fluoro-2,6-methoxy quinoline (0.18g, 40%) as pink solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.76-7.74 (d, J= 2.9Hz, 1H), 7.57-7.55 (d, *J* = 9 Hz, 1H) 7.25-7.22 (dd, *J* = 9 Hz, J= 2.9 Hz 1H), 7.00 (d, J= 2.9 Hz 1H), 4.12 (s, 3H), 3.93 (s, 3H). MS: MS *m/z* 208.1 (M^++1).

Scheme: Preparation of 1-Chloro-5-ethoxy- 6-methoxyisoquinoline



Step 1: Preparation of 5-bromo-1-chloro-6-methoxyisoquinoline

To a solution of 6-methoxy-1-chloroisoquinoline (2.5 g, 14.27 mmol) in acetonitrile (10 ml) was added *N*-bromosuccinimide ("NBS", 2.54 g, 14.27 mmol) at room temperature under argon atmosphere. The reaction mass was stirred at the same temperature for 2 h. The reaction mass was cooled to room temperature and

precipitated solid was collected by filtration to get crude 5-bromo-1-chloro-6-methoxyisoquinoline (2 g, 55.2%). The crude 5-bromo-1-chloro-6-methoxyisoquinoline was taken to the next step without further purification. MS: MS *m/z* 274.06 (M^++2).

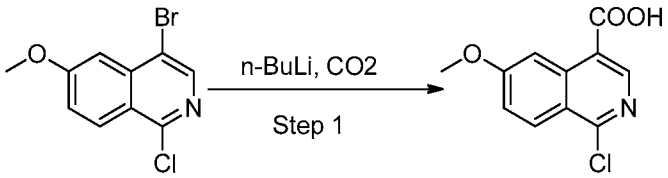
Step 2: Synthesis of 1-chloro-6-methoxyisoquinolin-5-ol

To a stirred solution of 5-bromo-1-chloro-6-methoxyisoquinoline (0.25 g, 0.917 mmol) in tetrahydrofuran (30 mL) under nitrogren and cooled to -78 °C was added n-butyllithium (1.147 mL, 1.835 mmol). The reaction mixture was stirred for 30 min, then to the solution was added triisopropylborate (0.426 mL, 1.835 mmol). The solution was stirred for 30 min. To the solution was added aq. 30% hydrogen peroxide (8.90 mmol, 1.5 mL), then aq. sodium hydroxide (0.917 mL, 0.917 mmol). The resulting mixture was stirred for 1h at rt. The reaction mixture was cooled to -40 °C, the to the mixture was added aq. sodium sulfite (1.156 g, 9.17 mmol). The resulting slurry was neutralized with 6N HCl solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate; filtered; then concentrated under reduced pressure. The crude sample was purified by silica gel chromatography using 20% ethyl acetate in pet ether to get 1-chloro-6-methoxyisoquinolin-5-ol (0.13 g, 0.608 mmol, 66.2 % yield) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.90 (s 1H), 8.13(d, J=8 Hz, 1H), 7.92(d, J=8 Hz, 1H), 7.80(d, J=12 Hz, 1H), 7.68(d, J=12 Hz, 1H), 4.02 (s 3H) MS: MS *m/z* 210.06 (M^++1).

Step 3: Synthesis of 1-chloro-5-ethoxy-6-methoxyisoquinoline

To a stirred solution of 1-chloro-6-methoxyisoquinolin-5-ol (0.13 g, 0.620 mmol) in acetonitrile (10 mL) at room temperature under nitrogen atmosphere was added potassium carbonate (0.257 g, 1.860 mmol) and iodoethane (0.100 mL, 1.240 mmol). The resulting solution was stirred at room temperature overnight. The volatiles were removed under reduced pressure. The resulting mixture was dissolved water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate; filtered; then concentrated under reduced pressure. The crude sample was purified by silica gel chromatography using 10% ethyl acetate in pet ether to get 1-chloro-5-ethoxy-6-methoxyisoquinoline (0.065 g, 0.268 mmol, 43.2 % yield) as solid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 1H MNMR DMSO-d6 8.20(d, J=4

Hz, 1H), 8.08(d, J=12 Hz,1H), 7.89(d, J=4 Hz,1H), 7.76(d, J=12 Hz,1H), 4.18 (q, J= 8 Hz, 2H), 4.01 (s 3H), 1.38 (t, J= 8 Hz, 3H). MS: MS *m/z* 230.11(M^++1).

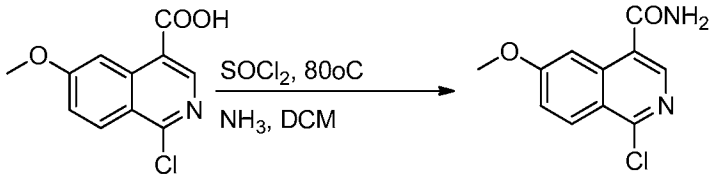


Step 1: Synthesis of 1-chloro-6-methoxyisoquinoline-4-carboxylic acid:

A solution of 4-bromo-1-chloro-6-methoxyisoquinoline (340 mg, 1.248 mmol) in THF (10 mL) was cooled to -78 °C. To the solution was added t-BuLi in pentane (1.715 mL, 2.74 mmol). The resulting colored solution was stirred at the same temperature for 20 min, then was transfered by syringe onto crushed dry ice (CO2) under nitrogen atmosphere. Once the dry ice had fully sublimed, the resulting solution was transferred to a separatory funnel and was diluted with water. The pH was adjusted to basic using 10% sodium hydroxide solution. The organic layer was separated and discarded. The aqueous phase was washed with ethyl acetate. The aqueous layer was then adjusted to pH 2.0 with aqueous HCl, then was twice extracted with EtOAc. The combined organic layers were washed with brine solution, dried over Na2SO4, filtered and concentrated in vacuo to afford 1-chloro-6-methoxyisoquinoline-4-carboxylic acid (140 mg, 0.589 mmol, 47.2 % yield) as light pink solid ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm : 13.60 (bs, 1 H), 8.82 (s, 1 H) 8.43-8.42 (d, *J*= 2.40 Hz, 1 H) 7.54-7.51 (dd, *J*=12.0, 2.4 Hz, 1 H) 3.97 (s, 3 H). MS: MS *m/z* 238.06 (M^++1).

Step 2: Synthesis of Methyl 1-chloro-6-methoxyisoquinoline-4-carboxylate:

Scheme: Preparation of 1-chloro-6-methoxyisoquinoline-4-carboxamide



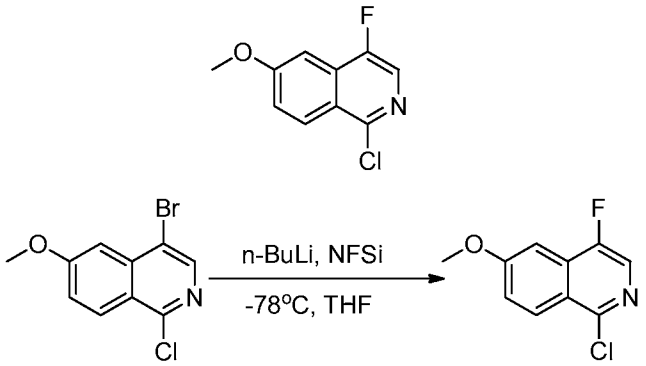
Synthesis of 1-chloro-6-methoxyisoquinoline-4-carboxamide:

To 1-chloro-6-methoxyisoquinoline-4-carboxylic acid (100 mg, 0.421 mmol) was added thionyl chloride (0.154 mL, 2.104 mmol) and the resulting suspension was

heated to reflux at 85 °C for 30 min. The volatiles were removed under reduced pressure. The resulting solid was dissolved in dichloromethane and this solution was then transferred to a -30 °C saturated solution of NH_3 (added via sparging) in dichloromethane (20 mL). The solution was allowed to warm to room temperature and was stirred for 1 h. The precipitate was isolated via filtration and dried to afford 1-chloro-6-methoxyisoquinoline-4-carboxylic acid (100 mg, 0.421 mmol). ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.41 (s, 1 H) 8.26 - 8.28 (m, 1 H) 7.85 (d, *J*=2.51 Hz, 1 H) 7.77 (br. s., 1 H) 7.50 (dd, *J*=9.29, 2.76 Hz, 1 H) 3.94 (s, 3 H). MS: MS *m/z* 237.1 (M^++1).

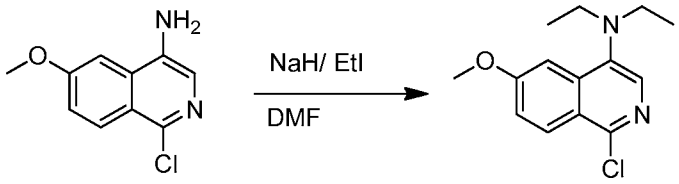
Preparation of 1-chloro-4-fluoro-6-methoxyisoquinoline

1-chloro-4-fluoro-6-methoxyisoquinoline



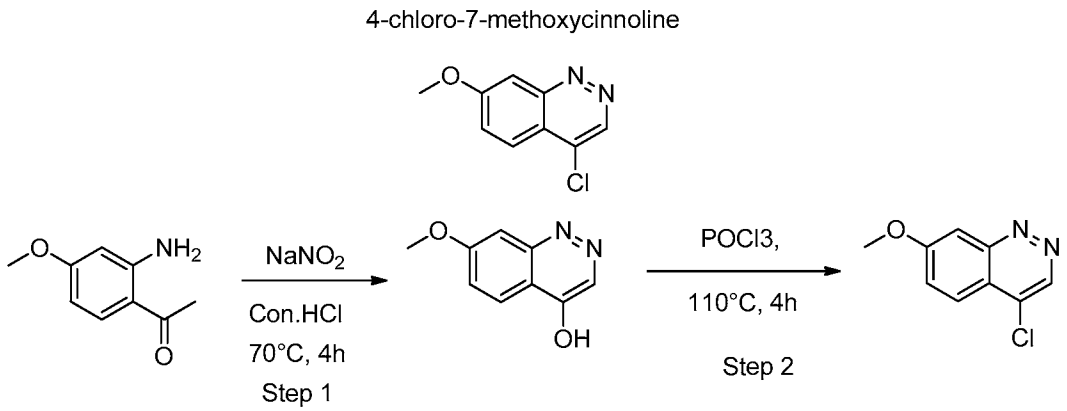
To a stirred solution of 4-bromo-1-chloro-6-methoxyisoquinoline (0.500 g, 1.835 mmol) in THF (10 mL) at -78 °C was added n-BuLi 1.6 M in hexanes (2.293 mL, 3.67 mmol). Stirred the reaction mixture for 1 h. Fluorodibenzenesulfonamide (0.579 g, 1.835 mmol) was added and the solution was stirred at the same temperature for 2h. to the solution was allowed to warm to room temperature with stirring and then was quenched via the addition of water. The volatiles were removed under reduced pressure and the resulting residue was dissolved in EtOAc and then washed with water; then brine solution; dried over anhydrous sodium sulphate; filtered; then concentrated under redued pressure to get crude compound. The crude compound was purified by silica gel chromatography eluting with 10% ethyl acetate in pet-ether to afford 1-chloro-4-fluoro-6-methoxyisoquinoline (0.2 g, 0.94 mmol) 51% as white solid. MS: MS *m/z* 212.5 (M^++1).

Preparation of 1-chloro-N,N-diethyl-6-methoxyisoquinolin-4-amine



To a two-neck round bottom flask under nitrogen atmosphere was added NaH (0.023 g, 0.959 mmol) and DMF (5 mL). The mixture was cooled to 0 °C. To the mixture was added 1-chloro-6-methoxyisoquinolin-4-amine (0.1 g, 0.479 mmol), and the mixture was stirred for 30 min. To the solution was added iodoethane (0.116 mL, 1.438 mmol); the mixture was stirred at room temperature for 18 h. The reaction mixture was poured onto ice, and the resulting mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate; filtered; then concentrated under reduced pressure. The crude sample was purified by silica gel chromatography using 10% ethyl acetate in Pet-ether as eluents to afford 1-chloro-N,N-diethyl-6-methoxyisoquinolin-4-amine (0.085 g, 0.308 mmol, 64.3 % yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.19 (d, *J*=9.25 Hz, 1 H) 7.91 (s, 1 H) 7.50 (d, *J*=2.55 Hz, 1 H) 7.23 - 7.29 (m, 2 H) 3.98 (s, 3 H) 3.20 (q, *J*=7.08 Hz, 4 H) 1.58 (s, 1 H) 1.08 (t, *J*=7.03 Hz, 6 H). MS: MS *m/z* 267.1 (M^++1).

Scheme: Preparation of 4-Chloro-7-methoxycinnolin



Step 1: Preparation of 7-methoxycinnolin-4-ol

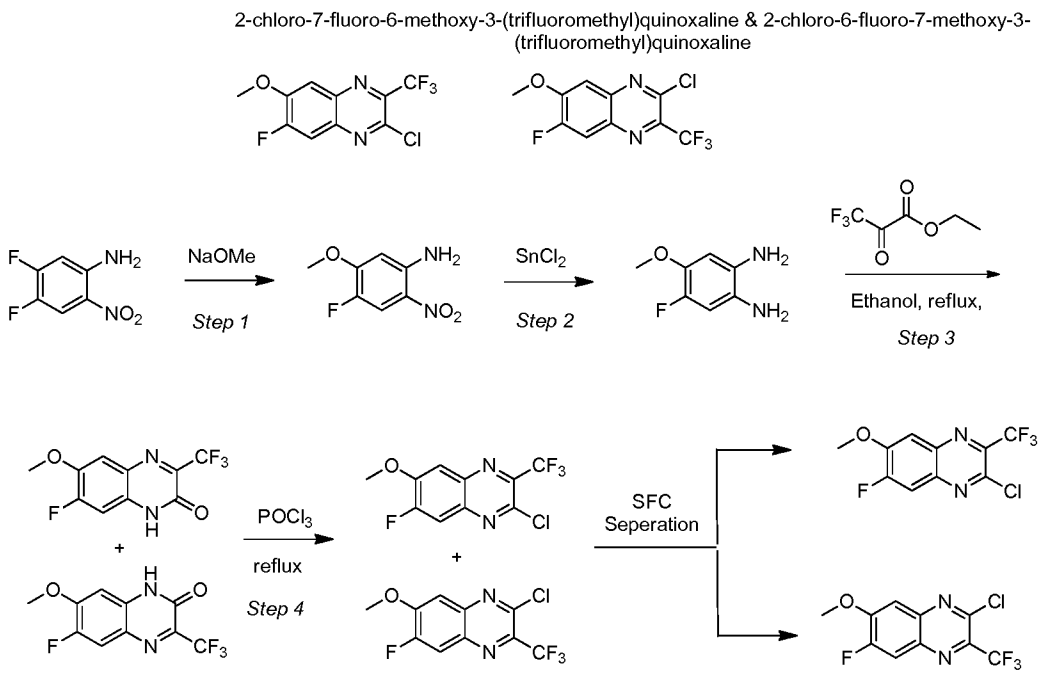
1-(2-amino-4-methoxyphenyl)ethanone (2.2 g, 13.32 mmol) was dissolved in aqueous concentrated HCl (40 mL) and then cooled to -5°C. To the solution was

added a solution of sodium nitrite (0.919 g, 13.32 mmol) in water (10 mL) over a period of 5 min. The mixture was stirred another 1h at 0°C and then heated to 70°C for 4h. The mixture was cooled to room temperature using an ice bath; the solid was collected by filtration. The wet solid was suspended in water (40 mL); and the solution was adjusted to pH ~12 using 4N NaOH solution to afford a brown solution. The solution was then adjusted to pH ~7 with concentrated aqueous HCl. A solid was precipitated and was collected via filtration, washing with water. The solution was dried to get 7-methoxycinnolin-4-ol (0.300 g, 1.703 mmol, 12.79 % yield) as brown solid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 13.29 (br. s., 1 H) 7.95 (d, *J*=9.04 Hz, 1 H) 7.67 (s, 1 H) 7.03 (dd, *J*=9.04, 2.01 Hz, 1 H) 6.90 (d, *J*=2.51 Hz, 1 H) 3.90 (s, 3 H). MS: MS *m/z* 177 (M^++1).

Step 2: Preparation of 4-Chloro-7-methoxycinnoline

A suspension of 7-methoxycinnolin-4-ol (0.490 g, 2.78 mmol) in $POCl_3$ (10 mL, 107 mmol) was heated to 110°C for 4 h. Removed the volatiles under reduced pressure; resulting residue was poured onto crushed ice. The solution was adjusted to pH ~8 using 10% sodium bicarbonate solution; then extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulphate; filtered; then concentrated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography eluting with 40 % ethyl acetate in pet-ether to afford 4-chloro-7-methoxycinnoline (0.270 g, 1.387 mmol, 49.9 % yield) as brown solid. ^{1}H NMR (400 MHz, CDCl3): δ ppm 9.23 (s, 1 H) 8.08 (d, *J*=9.26 Hz, 1 H) 7.78 (d, *J*=2.50 Hz, 1 H) 7.50 (dd, *J*=9.26, 2.50 Hz, 1 H) 4.05 (s, 3 H). MS: MS *m/z* 195.1 (M^++1).

Scheme: Preparation of 2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline and 2-chloro-6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxaline



Step 1: Preparation of 4-fluoro-5-methoxy-2-nitroaniline

To an ice cooled 100 ml round bottom flask charged with methanol (30 mL) was added sodium methoxide (1.551 g, 28.7 mmol). After the solution was homogeneous, 4,5-difluoro-2-nitroaniline (2 g, 11.49 mmol) was added portion wise. The solution turns a bright yellow and slowly yellow precipitation was observed. Solvent was removed under reduced pressure and the residue was diluted with water and acidified using 1.5N HCl solution. The aqueous layer was extracted with ethyl acetate twice; the combined organics were washed with water; then brine solution; dried over anhydrous sodium sulphate; filtered; then concentrated to dryness to get 4-fluoro-5-methoxy-2-nitroaniline (1.8 g, 9.48 mmol, 82 % yield) as pale yellow solid. ^{1}H NMR (400 MHz, CDCl3): δ ppm 7.76 (d, *J*=12.55 Hz, 1 H) 7.54 (br. s., 2 H) 6.65 (s, 1 H) 3.86 (s, 3H). ^{19}F NMR: δ ppm -147.64 (1F); MS: MS *m/z* 185.2 (M^{+}-1).

Step 2: Preparation of 4-fluoro-5-methoxybenzene-1,2-diamine

To a suspension of tin(II) chloride di-hydrate (6.55 g, 29.0 mmol) in water (40 mL) was slowly added aqueous concentrated HCl (8 mL), and the resulting solution was stirred for 10 min. 5-fluoro-4-methoxy-2-nitroaniline (1.8 g, 9.67 mmol) was added portion wise to the reaction mass, and the reaction mixture was then stirred at

70 °C overnight. The solution was allowed to cool to room temperature and was adjusted to pH = 10-11 via drop wise addition of 10% NaOH solution. The aqueous mixture was extracted with ethyl acetate. The combined organics were washed with water; then brine; dried over anhydrous sodium sulphate; filtered; then concentrated to afford crude 4-fluoro-5-methoxybenzene-1,2-diamine (1.2 g, 7.68 mmol, 79 % yield) as brown solid. The crude compound was taken to the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 6.32 - 6.43 (m, 2 H) 4.32 (br. s., 4 H) 3.65(s, 3H); ^{19}F NMR: δ ppm -149.03 (1F); MS: MS *m/z* 157.3 (M^{+}+1).

Step 3: Preparation of 7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one and 6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one

To a solution of 4-fluoro-5-methoxybenzene-1,2-diamine (13 g, 83 mmol) in ethanol (100 mL) was added ethyl 3,3,3-trifluoro-2-oxopropanoate (13.15 mL, 108 mmol) at room temperature. The reaction mass was heated at reflux for 18 h. The solvent was evaporated under reduced pressure and the residue was washed with diethyl ether to get crude compound 7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxalin-2-ol (15 g, 49.2 mmol, 59.1 % yield) as mixture of regioisomer. The crude compound was taken directly to the next step without separation of isomers. MS: MS *m/z 263.1* (M^{+}+1).

Step 4: Preparation of 2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline and 2-chloro-6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxaline

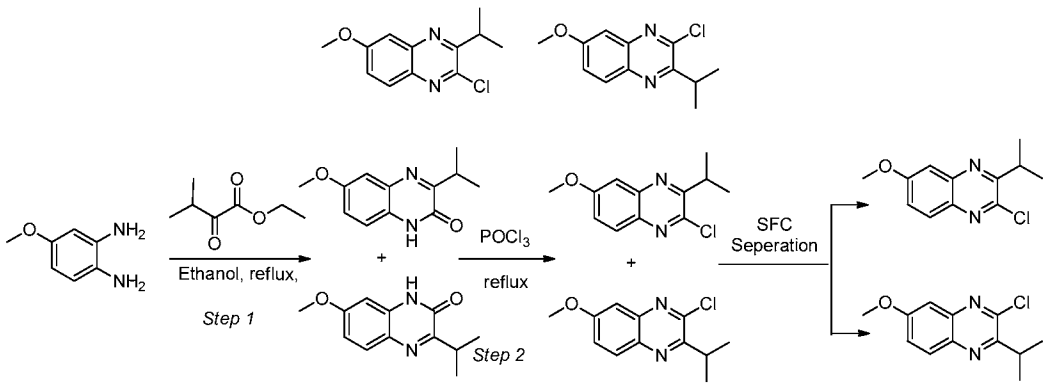
A solution of 7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxalin-2-ol (12 g, 45.8 mmol) in $POCl_3$ (100 mL) was heated at reflux for 3 h. Excess $POCl_3$ was removed under reduced pressure and the residue was diluted with cold water and basified by using 10% NaOH Solution (pH = ~10). The aqueous reaction mass was extracted with ethyl acetate. The combined organic layers were washed with water; then brine; dried over anhydrous sodium sulphate; filtered; then concentrated to get crude compound as mixture of regioisomer. The mixture of regioisomer was separated by SFC to get 2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline (3.5 g, 12.22 mmol, 26.7 % yield) and 2-chloro-6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxaline (5 g, 17.46 mmol, 38.1 % yield).

2-chloro-6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxaline: ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.83-7.81 (d, *J*=10.4 Hz, 1 H) 7.46-7.44 (d, *J*=8 Hz, 1 H), 4.09 (s, 3 H). ^{19}F NMR: δ ppm -66.32 (3F), -122.46 (1F). The structure was confirmed by

single crystal x-ray studies.

2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline: ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.73-7.71 (d, *J*=10.8 Hz, 1 H) 7.58-7.56 (d, *J*=8.4 Hz, 1 H), 4.08 (s, 3 H). ^{19}F NMR: δ ppm -66.58 (3F), -119.04 (1F).

Scheme: Preparation of Synthesis of 2-chloro-3-isopropyl-6-methoxyquinoxaline & 3-chloro-2-isopropyl-6-methoxyquinoxaline



Step 1: Preparation of 3-isopropyl-6-methoxyquinoxalin-2(1H)-one and 3-isopropyl-7-methoxyquinoxalin-2(1H)-one

The same procedure was followed as described for 7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one but methoxybenzene-1,2-diamine and ethyl 3-methyl-2-oxobutanoate were used as starting material instead of 4-fluoro-5-methoxybenzene-1,2-diamine and ethyl 3,3,3-trifluoro-2-oxopropanoate. MS: MS m/z 219.1 (M^++1).

Step 2: Preparation of 2-chloro-3-isopropyl-6-methoxyquinoxaline and 3-chloro-2-isopropyl-6-methoxyquinoxaline

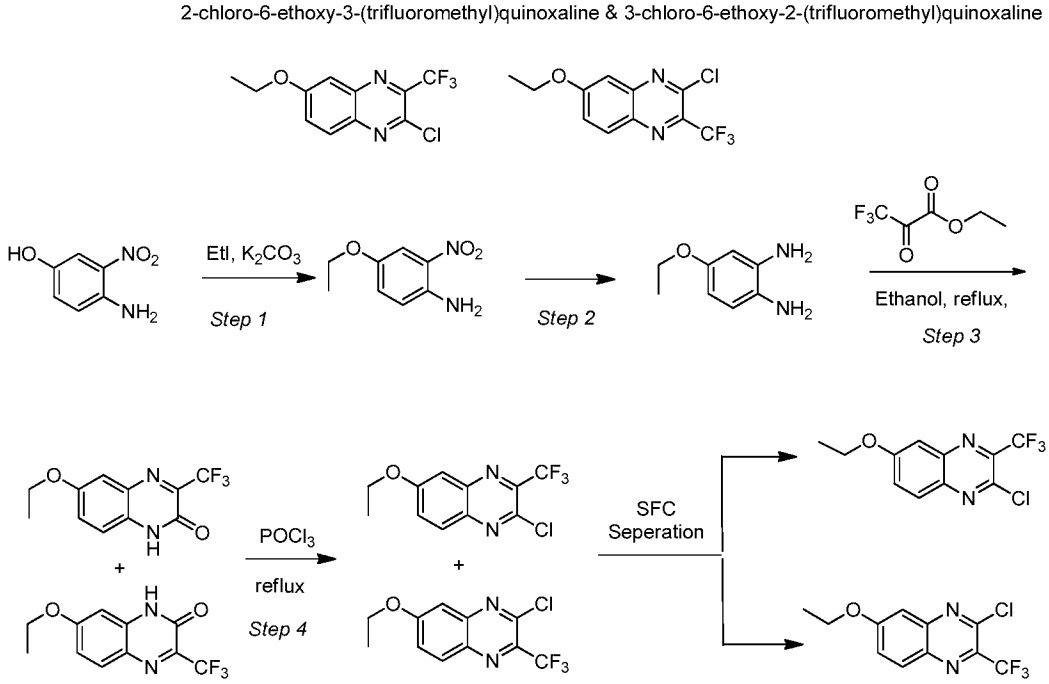
The same procedure was followed as described for *2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline* but 3-isopropyl-6-methoxyquinoxalin-2(1H)-one and 3-isopropyl-7-methoxyquinoxalin-2(1H)-one were used as starting material instead of *2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline and 2-chloro-6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxaline.*

3-chloro-2-isopropyl-6-methoxyquinoxaline: ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm ^{1}H NMR (400 MHz, $CDCl_3$): 7.94 (d, J= 9.2 Hz, 1H) 7.38-7.35 (dd, J= 9.2 Hz,2.8Hz,

1H) 7.27-7.26 (m, 1H) 3.91 (s, 3H) 3.70-3.63 (m, 1H) 1.40 (d, J= 8 Hz, 6H). MS: MS m/ z 237.05 (M^++1).

2-chloro-3-isopropyl-6-methoxyquinoxaline: MS: MS m/ z 237.06 (M^++1).

Scheme: Preparation of 2-chloro-6-ethoxy-3-(trifluoromethyl)quinoxaline and 3-chloro-6-ethoxy-2-(trifluoromethyl)quinoxaline



Step 1: Preparation of 4-ethoxy-2-nitroaniline

To a solution of 4-amino-3-nitrophenol (5.0 g, 32.4 mmol) in acetonitrile (100 mL) was added K_2CO_3 (13.45 g, 97 mmol) followed by ethyl iodide (13.11 mL, 162 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. The reaction mixture was filtered through celite bed and washed with acetonitrile. The filtrate was evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography using 10-30% ethyl acetate in hexane as mobile phase to get 4-ethoxy-2-nitroaniline (3.0 g, 16.47 mmol, 50.8 % yield) as red color solid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.35-7.34(d, *J* =4 Hz, 1H), 7.23 (s, 2H), 7.16-7.13 (dd, *J* = 9.2 Hz, 3.2 Hz, 1H), 7.00 – 6.97 (d, *J* =9.6 Hz, 1H), 3.99 – 3.94 (q, *J* =6.8 Hz, 6H), 1.31 – 1.28 (t, *J* =6.8 Hz ,

3H). MS: MS *m/z* 181.2 (M^+-1).

Step 2: Preparation of 4-ethoxybenzene-1,2-diamine

The same procedure was followed as discribed for *4-fluoro-5-methoxybenzene-1,2-diamine* but 4-ethoxy-2-nitroaniline used as starting materials instead of *4-fluoro-5-methoxy-2-nitroaniline.* ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 6.40-6.38 (d, *J* =8 Hz, 1H), 6.15–6.14 (d, *J* =3.6 Hz, 1H), 5.97-5.93 (dd, *J* =11.2 Hz, 3.6 Hz, 1H), 4.45 (bs, 2H), 3.975-3.970 (bs,, 2H), 3.84–3.77 (q, *J* =9.2 Hz, 2H), 1.29–1.21 (t, *J* =16.4 Hz , 3H).

Step 3: Preparation of 6-ethoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one and 7-ethoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one

The same procedure was followed as described for *7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one* but 4-ethoxybenzene-1,2-diamine was used as starting material instead of 4-fluoro-5-methoxybenzene-1,2-diamine. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 12.92(br, s, 2H), 7.84-7.81(d, *J* =12 Hz, 1H), 7.44-7.33 (m, 4H), 7.82 (s, 1H), 3.87(s, 6H), MS: MS *m/z 245.15* (M^++1).

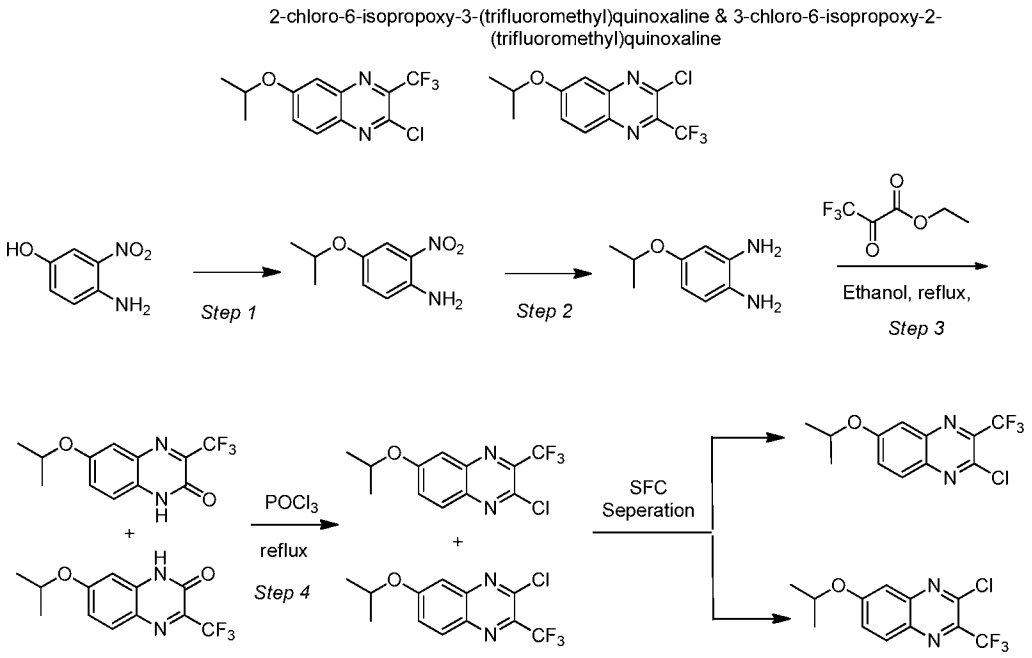
Step 4: Preparation of 2-chloro-6-ethoxy-3-(trifluoromethyl)quinoxaline and 3-chloro-6-ethoxy-2-(trifluoromethyl)quinoxaline

The same procedure was followed as discribed for *2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline* but 6-ethoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one and 7-ethoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one was used as starting material instead of *2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline and 2-chloro-6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxaline.*

2-chloro-6-ethoxy-3-(trifluoromethyl)quinoxaline : ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.10-8.07 (d, *J* = 12 Hz, 1H), 7.75-7.44 (m, 2H), 3.95 (s, 3H); ^{19}F NMR: δ ppm -65.36(1F) MS: MS *m/z* 263.10 (M^++1).

3-chloro-6-ethoxy-2-(trifluoromethyl)quinoxaline : ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.11-8.08 (d, *J* = 12 Hz, 1H), 7.78-7.75 (d, *J* = 12 Hz, 1H), 7.68 (s, 1H), 4.00 (s, 3H). ^{19}F NMR: δ ppm -65.36(1F) MS: MS *m/z* 263.09 (M^++1).

Scheme: Preparation of 2-chloro-6-isopropoxy-3-(trifluoromethyl)quinoxaline & 3-chloro-6-isopropoxy-2-(trifluoromethyl)quinoxaline



Step 1: Preparation of 4-isopropoxy-2-nitroaniline

To a solution of 4-amino-3-nitrophenol (5 g, 32.4 mmol) in DMF (30 mL) was added Cesium carbonate (21.14 g, 64.9 mmol) and 2-Bromopropane (3.05 mL, 32.4 mmol) at room temperature. The reaction mass was heated at 80 °C for 3 h. Solvent was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic solution was washed with water, dried over anhydrous sodium sulphate and concentrated to get the crude compound. The crude compound was purified using silica gel flash column chromatography eluting with 30% ethyl acetate in pet-ether to afford 4-isopropoxy-2-nitroaniline (6 g, 26.9 mmol, 83 % yield) as a brown crystalline solid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.37 (d, *J*=2.51 Hz, 1 H) 7.21 (s, 2 H) 7.14 (dd, *J*=9.29, 2.76 Hz, 1 H) 6.99 (d, *J*=9.04 Hz, 1 H) 4.38 - 4.52 (m, 1 H) 1.13 - 1.31 (m, 6 H) MS: MS *m/z* 197.15 (M^++1).

Step 2: Preparation of 4-isopropoxybenzene-1,2-diamine

The same procedure was followed as discribed for *4-fluoro-5-methoxybenzene-1,2-diamine* but 4-isopropoxy-2-nitroaniline was used as starting materials instead of *4-fluoro-5-methoxy-2-nitroaniline.* ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 6.39 (d, *J*=8.31 Hz, 1 H) 6.15 (d, *J*=3.02 Hz, 1 H) 5.96 (dd, *J*=8.31, 2.64

Hz, 1 H) 4.36 (bs, 2 H) 4.19 - 4.32 (m, 1 H) 3.9 (bs, 2H) 1.17 (d, *J*=6.04 Hz, 6 H) MS: MS *m/z 167.1*(M^++1).

Step 3: Preparation of 6-isopropoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one and 7-isopropoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one

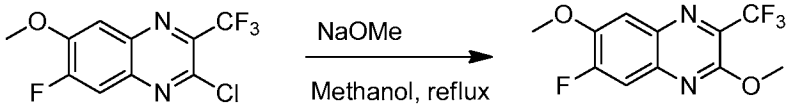
The same procedure was followed as discribed for *7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one* but 4-isopropoxybenzene-1,2-diamine was used as starting material instead of 4-fluoro-5-methoxybenzene-1,2-diamine. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 12.98 (s, 1 H) 7.40-7.31 (m, 3 H) 4.73 (m, 1 H) 4.19 - 4.32 (m, 1 H) 1.28 (m, 6 H) ^{19}F NMR: δ ppm -67.86(3F) MS: MS *m/z 273.1*(M^++1).

Step 4: Preparation of 2-chloro-7-isopropoxy-3-(trifluoromethyl)quinoxaline

The same procedure was followed as discribed for *2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline* but 6-isopropoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one and 7-isopropoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one was used as starting material instead of *2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline and 2-chloro-6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxaline.* ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.04 - 8.20 (m, 1 H) 7.55 - 7.75 (m, 2 H) 4.92 - 5.05 (m, 1 H) 1.33 - 1.43 (m, 6 H) ^{19}F NMR: δ ppm -66.10 (3F) MS: MS *m/z 291.5*(M^++1). Structure was confirmed by single crystal X-ray studies.

Preparation of 6-fluoro-3,7-dimethoxy-2-(trifluoromethyl)quinoxaline

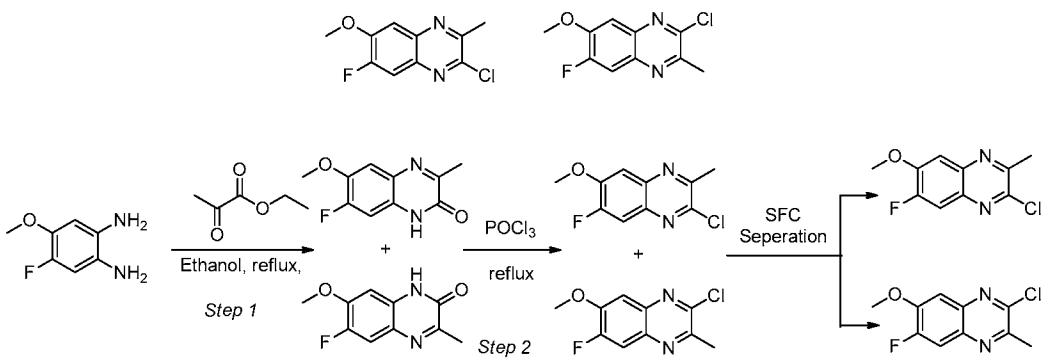
6-fluoro-3,7-dimethoxy-2-(trifluoromethyl)quinoxaline



To a solution of 2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline (0.7 g, 2.49 mmol) in Methanol (20 ml) was added Sodium methoxide (0.135 g, 2.495 mmol) at room temperature under nitrogen atmosphere. The reaction mass was heated at reflux for 3 h. The solvent was evaporated under reduced pressure and the residue was diluted with dichloromethane and washed with water. The organic layer was dried over anhydrous sodium sulphate and evaporated to get crude compound 7-fluoro-2-methoxyquinoxaline (0.45 g, 58.8 % yield) as white solid. ^{1}H NMR (400

MHz, $CDCl_3$): δ ppm 7.57-7.51 (m, 2H), 4.15 (s, 3H), 4.02 (s, 3H); ^{19}F NMR: δ ppm -67.89 (3F), -122.93 (1 F).

Scheme: Preparation of 2-chloro-7-fluoro-6-methoxy-3-methylquinoxaline & 2-chloro-6-fluoro-7-methoxy-3-methylquinoxaline



Step 1: Preparation of 7-fluoro-6-methoxy-3-methylquinoxalin-2(1H)-one and 6-fluoro-7-methoxy-3-methylquinoxalin-2(1H)-one

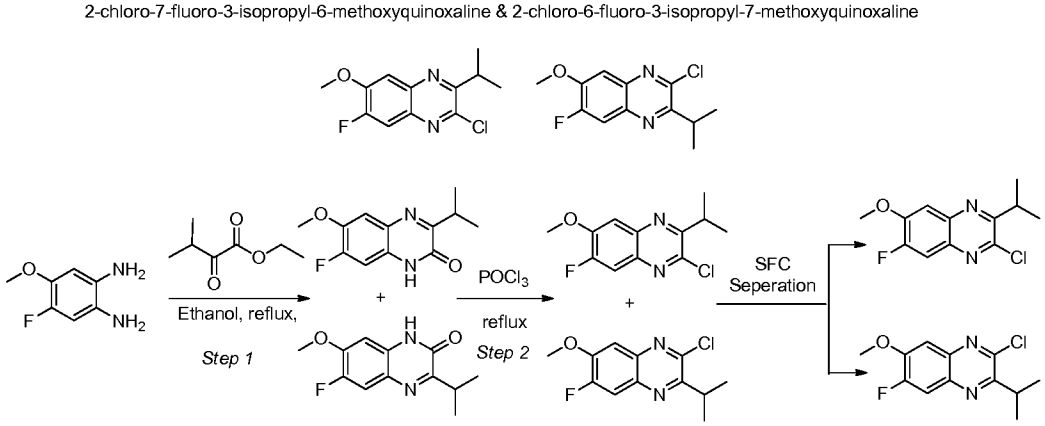
The same procedure was followed as discribed for *7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one* but ethyl 2-oxopropanoate was used as starting material instead of ethyl 3,3,3-trifluoro-2-oxopropanoate. ^1H NMR (400 MHz, DMSO-d6): δ ppm 12.27 (s, 1 H) 7.57 (d, J=11.6 Hz,1 H) 7.21-6.91 (m, 1 H) 3.92 (m, 6 H) ^{19}F NMR: δ ppm -123.21(1F) MS: MS *m/z* 209.1(M^++1).

Step 2: Preparation of 2-chloro-7-fluoro-6-methoxy-3-methylquinoxaline and 2-chloro-6-fluoro-7-methoxy-3-methylquinoxaline

The same procedure was followed as discribed for *2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline* but 7-fluoro-6-methoxy-3-methylquinoxalin-2(1H)-one and 6-fluoro-7-methoxy-3-methylquinoxalin-2(1H)-one was used as starting material instead of *2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline and 2-chloro-6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxaline* ^1H NMR (400 MHz, $CDCl_3$): δ ppmδ ppm 7.90 (d, J=12 Hz, 1 H) 7.63 (d, J=8.8 Hz, 1 H) 4.02 (s, 3H) 2.71 (s, 3 H) ^{19}F NMR: δ ppm -121.93(1F) MS: MS *m/z* 227.0 (M^++1). *and for 2-chloro-6-fluoro-7-methoxy-3-methylquinoxaline :* ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.61 (d, J=11.2 Hz, 1 H)

7.41 (d, J=8.4 Hz, 1 H) 4.05 (s, 3H) 2.79 (s, 3 H) ^{19}F NMR: δ ppm -125.42(1F) MS: MS *m/ z 227.0*(M^++1).

Scheme: Preparation of 2-chloro-7-fluoro-3-isopropyl-6-methoxyquinoxaline & 2-chloro-6-fluoro-3-isopropyl-7-methoxyquinoxaline



Step 1: Preparation of 7-fluoro-3-isopropyl-6-methoxyquinoxalin-2(1H)-one and 6-fluoro-3-isopropyl-7-methoxyquinoxalin-2(1H)-one

The same procedure was followed as described for *7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one* but ethyl 3-methyl-2-oxobutanoate was used as starting material instead of *ethyl 3,3,3-trifluoro-2-oxopropanoate*. MS: MS m/ z 237.1 (M^++1).

Step 2: Preparation of 2-chloro-3-isopropyl-6-methoxyquinoxaline and 3-chloro-2-isopropyl-6-methoxyquinoxaline

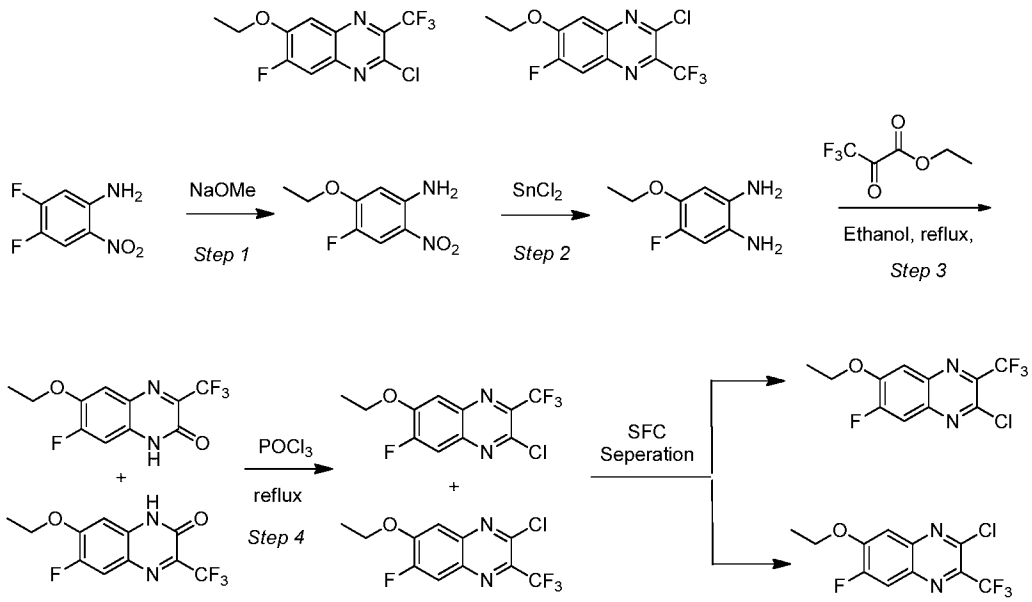
The same procedure was followed as discribed for *2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline* but 7-fluoro-3-isopropyl-6-methoxyquinoxalin-2(1H)-one and 6-fluoro-3-isopropyl-7-methoxyquinoxalin-2(1H)-one was used as starting material instead of *7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one and 6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one.*

2-chloro-7-fluoro-3-isopropyl-6-methoxyquinoxaline: ^{1}H NMR (400 MHz, $CDCL_3$): δ ppm 7.69-7.66 (d, *J* = 12 Hz, 1H), 7.36-7.34 (d, *J* = 8 Hz, 1H), 4.05 (s, 3H), 3.66 (m, 1 H), 1.39-1.37 (d, *J* = 9 Hz, 6H). ^{19}F NMR: δ ppm -126.92(1F) MS: MS *m/ z* 255.1 (M^++1).

2-chloro-6-fluoro-3-isopropyl-7-methoxyquinoxaline: ^{1}H NMR (400 MHz, $CDCL_3$): δ ppm 7.69-7.66 (d, *J* = 12 Hz, 1H), 7.36-7.34 (d, *J* = 8 Hz, 1H), 4.05 (s, 3H), 3.66 (m, 1 H), 1.39-1.37 (d, *J* = 9 Hz, 6H). ^{19}F NMR: δ ppm -126.92(1F) MS: MS *m/z* 255.1 (M^++1).

Scheme: Preparation of 2-chloro-6-ethoxy-7-fluoro-3-(trifluoromethyl)quinoxaline & 2-chloro-7-ethoxy-6-fluoro-3- (trifluoromethyl)quinoxaline

2-chloro-6-ethoxy-7-fluoro-3-(trifluoromethyl)quinoxaline & 2-chloro-7-ethoxy-6-fluoro-3-(trifluoromethyl)quinoxaline



Step 1: Preparation of 5-ethoxy-4-fluoro-2-nitroaniline

The same procedure was followed as discribed for 4-fluoro-5-methoxy-2-nitroaniline but sodium ethoxide was used instead *sodium methoxide:* ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.77-7.74 (d, *J*=12.4 Hz, 1 H) 6.64-6.62 (d, *J*= 8 Hz, 1 H) 4.15-4.09 (q, *J*=7.2 Hz, 2 H) 1.40-1.37 (t, *J*= 7.2 Hz, 3 H). ^{19}F NMR: δ ppm -144.19 (1F); MS: MS *m/z* 201.1 (M^++1).

Step 2: Preparation of 4-ethoxy-5-fluorobenzene-1,2-diamine

The same procedure was followed as discribed for *4-fluoro-5-methoxybenzene-1,2-diamine* but 5-ethoxy-4-fluoro-2-nitroaniline was used instead of *4-fluoro-5-methoxy-2-nitroaniline*. MS: MS *m/z* 271.1 (M^++1).

Step 3: Preparation of 6-ethoxy-7-fluoro-3-(trifluoromethyl)quinoxalin-2(1H)-one and 7-ethoxy-6-fluoro-3-(trifluoromethyl)quinoxalin-2(1H)-one

The same procedure was followed as discribed for *7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one and 6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one* but 4-ethoxy-5-fluorobenzene-1,2-diamine was used instead of *4-fluoro-5-methoxybenzene-1,2-diamine*. MS: MS *m/z* 277.1 (M^++1).

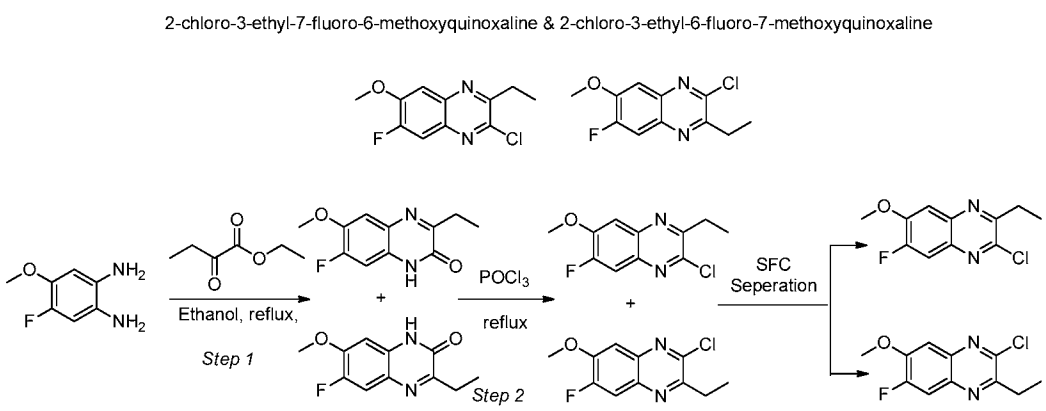
Step 4: Preparation of 2-chloro-7-ethoxy-6-fluoro-3-(trifluoromethyl)quinoxaline and 2-chloro-6-ethoxy-7-fluoro-3-(trifluoromethyl)quinoxaline

The same procedure was followed as discribed for *2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline and 2-chloro-6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxaline* but 6-ethoxy-7-fluoro-3-(trifluoromethyl)quinoxalin-2(1H)-one and 7-ethoxy-6-fluoro-3-(trifluoromethyl)quinoxalin-2(1H)-one was used as a starting material instead of *7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one and 6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one.*

2-chloro-7-ethoxy-6-fluoro-3-(trifluoromethyl)quinoxaline: ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.22-8.19 (d, *J* = 11.2 Hz, 1H), 7.82-7.80 (d, *J* = 8.4 Hz, 1H), 4.43-4.38 (q, *J* = 6.8 Hz, 1H, 2H), 1.49-1.45 (t, *J* = 7.2 Hz, 1H, 3H); ^{19}F NMR: δ ppm -64.96(3F), -122.87 (1F). MS: MS *m/z* 295.1 (M^++1).

2-chloro-6-ethoxy-7-fluoro-3-(trifluoromethyl)quinoxaline: MS: MS *m/z* 295.1 (M^++1).

Scheme: Preparation of 2-chloro-3-ethyl-7-fluoro-6-methoxyquinoxaline & 2-chloro-3-ethyl-6-fluoro-7-methoxyquinoxaline



Step 1: Preparation of 3-ethyl-7-fluoro-6-methoxyquinoxalin-2(1H)-one and 3-ethyl-6-fluoro-7-methoxyquinoxalin-2(1H)-one

The same procedure was followed as described for *7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one* but ethyl 2-oxobutanoate was used as starting material instead of *ethyl 3,3,3-trifluoro-2-oxopropanoate*. MS: MS m/ z 223.1 (M^++1).

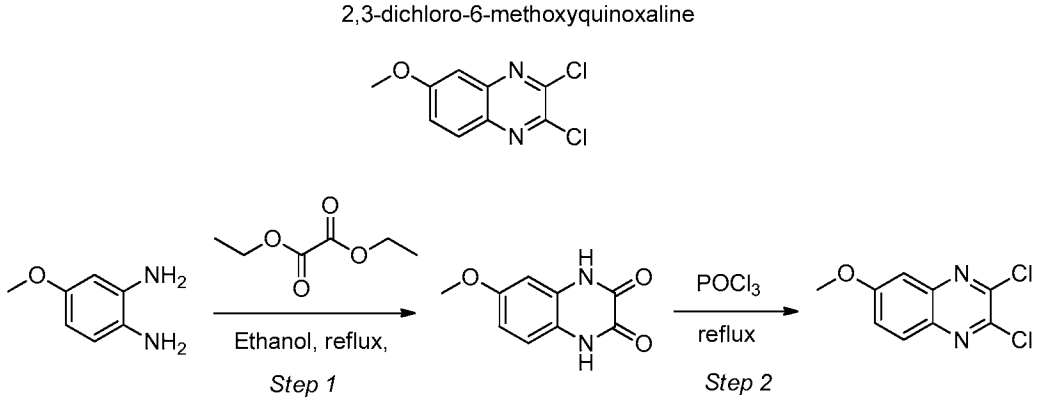
Step 2: Preparation of 2-chloro-3-ethyl-7-fluoro-6-methoxyquinoxaline and 2-chloro-3-ethyl-6-fluoro-7-methoxyquinoxaline

The same procedure was followed as discribed for *2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline* but 3-ethyl-7-fluoro-6-methoxyquinoxalin-2(1H)-one and 3-ethyl-6-fluoro-7-methoxyquinoxalin-2(1H)-one was used as starting material instead of *7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one and 6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one*

2-chloro-3-ethyl-7-fluoro-6-methoxyquinoxaline: ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.62 (d, *J*= 11.2 Hz, 1 H), 7.45 (d, *J*= 8.4 Hz, 1 H), 4.04 (s, 3 H), 3.15-3.10 (q, *J*= 7.6 Hz, 2 H), 1.43 (t, *J*=7.6 Hz, 3 H). ^{19}F NMR: δ ppm – 126.58 (1F). MS: MS *m/ z* 241.1 (M^++1)

2-chloro-3-ethyl-6-fluoro-7-methoxyquinoxaline: MS: MS *m/ z* 241.1 (M^++1)

Scheme: Preparation of 2,3-dichloro-6-methoxyquinoxaline



Step 1: Preparation of 6-methoxyquinoxaline-2,3(1H,4H)-dione

The same procedure was followed as discribed for *7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxalin-2(1H)-one* but diethyl oxalate was used as starting

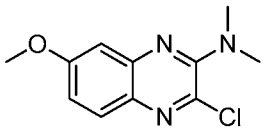
material instead of ethyl 3,3,3-trifluoro-2-oxopropanoate. ^{1}H NMR (400 MHz, DMSO-d6) 11.84 (s, 1H) 9.68 (bs , 1H) 7.09-7.04 (m, 3H) 3.71 (s, 3H) MS: MS *m/z* 193.01 (M^++1).

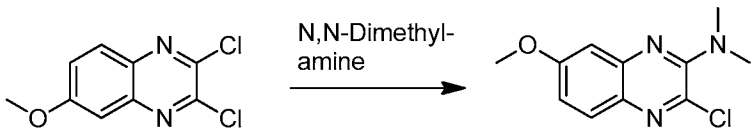
Step 2: Preparation of 2,3-dichloro-6-methoxyquinoxaline

The same procedure was followed as discribed for *2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline* but 6-methoxyquinoxaline-2,3(1H,4H)-dione was used as starting material instead of *2-chloro-7-fluoro-6-methoxy-3-(trifluoromethyl)quinoxaline and 2-chloro-6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxaline.* ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.91 (d, J=9.2 Hz, 1 H) 7.41 (dd, J=9.2, 2.8 Hz, 1 H) 7.30 (d, J=2.8Hz , 1H) 3.96 (s, 3H).

Preparation of 3-chloro-7-methoxy-N,N-dimethylquinoxalin-2-amine

3-chloro-7-methoxy-*N*,*N*-dimethylquinoxalin-2-amine



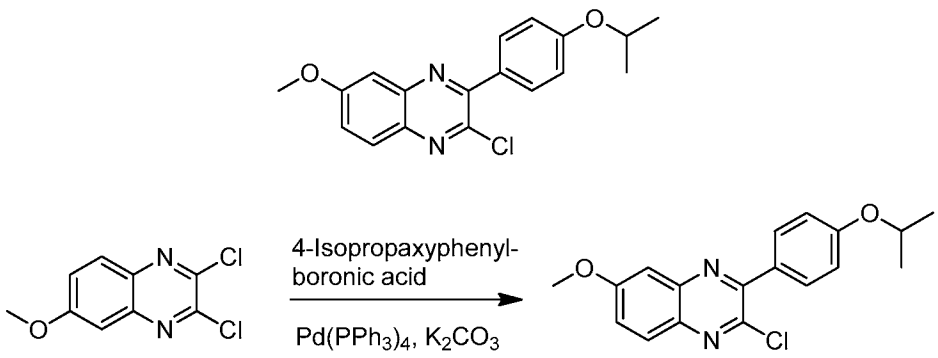


Preparation of 3-chloro-7-methoxy-N,N-dimethylquinoxalin-2-amine

A stirred solution of 2,3-dichloro-6-methoxyquinoxaline (200mg, 0.873 mmol) in aqueous 40% *N,N*-dimethyl amine was heated in a sealed tube at 100 °C for 10 min. The reaction mass was cooled to room temperature and diluted with DCM. The solution was washed with water; then brine solution; dried over sodium sulphate and evaporated to get crude compound. The crude compound was purified by silica gel chromatography (5% EtOAc in pet-ether) to get 3-chloro-7-methoxy-*N,N*-dimethylquinoxalin-2-amine (200 mg, 0.825 mmol, 94 %) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) 7.73 (d, J=10 Hz, 1H) 7.12-7.10 (m, 2H) 3.92 (s, 3H) 3.17 (s, 6H). MS: MS *m/z* 238.14 (M^++1). Structure was confirmed by single crystal X-ray studies.

Preparation of 2-chloro-3-(4-isopropoxyphenyl)-6-methoxyquinoxaline

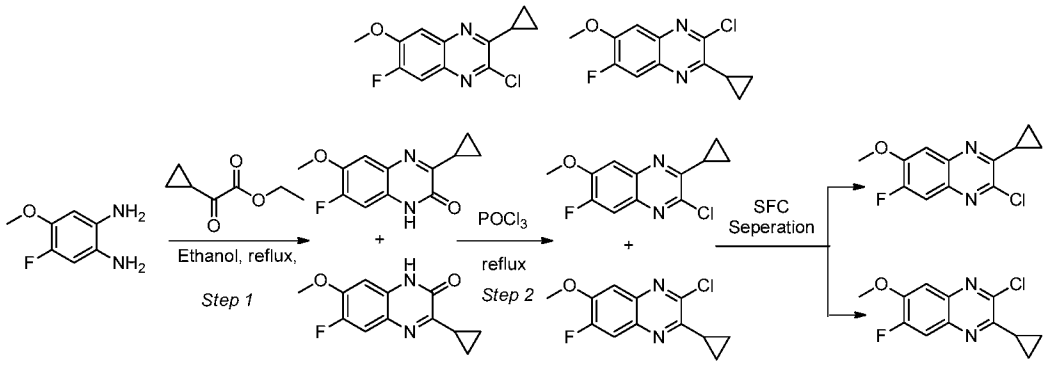
2-chloro-3-(4-isopropoxyphenyl)-6-methoxyquinoxaline



To a solution of 2,3-dichloro-6-methoxyquinoxaline (100 mg, 0.437 mmol) in dioxane (10 mL) and water (2 mL) was added (4-isopropoxyphenyl)boronic acid (79 mg, 0.437 mmol) followed by K_2CO_3 (121 mg, 0.873 mmol) at room temperature. The resulting reaction mass was degassed with nitrogen for 30 min. $Pd(PPh_3)_4$ (25.2 mg, 0.022 mmol) was added to the reaction mixture and the mixture was then heated in a pressure tube at 90 ° C for 16 h. The mixture was allowed to cool to room temperature; then was diluted with ethyl acetate. The organic solution was washed with water; then brine; dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% EtOAc in pet ether) to afford 2-chloro-3-(4-isopropoxyphenyl)-6-methoxyquinoxaline (70 mg, 0.192 mmol, 43.9 % yield) as a off white solid. ^1H NMR (400 MHz, $CDCl_3$): 7.83 (m, 1 H) 7.82 (m, 2 H) 7.42 (m, 2 H) 7.03 (m, 2 H) 4.68-4.62 (m, 1 H) 3.97 (s, 3 H) 1.30 (m, 6 H) MS: MS *m/z* 329.56 (M^++1). The structure of the compound was confirmed by single crystal x-ray studies.

Preparation of Synthesis of 2-chloro-3-cyclopropyl-7-fluoro-6-methoxyquinoxaline and 2-chloro-3-cyclopropyl-6-fluoro-7-methoxyquinoxaline

Synthesis of 2-chloro-3-cyclopropyl-7-fluoro-6-methoxyquinoxaline and 2-chloro-3-cyclopropyl-6-fluoro-7-methoxyquinoxaline



Step 1: Preparation of 3-cyclopropyl-7-fluoro-6-methoxyquinoxalin-2-ol and 3-cyclopropyl-6-fluoro-7-methoxyquinoxalin-2-ol

To a stirred solution of 4-fluoro-5-methoxybenzene-1,2-diamine (0.800 g, 5.12 mmol) in ethanol (10 mL) was added ethyl 2-cyclopropyl-2-oxoacetate (0.874 g, 6.15 mmol). The reaction mixture was stirred for 12 h at 80 °C. The reaction mixture was concentrated under reduced pressure to get a crude mixture of 3-cyclopropyl-7-fluoro-6-methoxyquinoxalin-2-ol and 3-cyclopropyl-6-fluoro-7-methoxyquinoxalin-2-ol compound. This crude mixture was directly used for the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.29 (s, 1 H) 6.95 (m, 3 H) 4.30 (m, 4 H) 3.89 (m, 3 H) 3.80 (m, 2 H) 2.26 (m, 1 H) 1.29 (m, 8 H). MS: MS *m/z* 235.1 (M^++1).

Step 2: Preparation of 2-chloro-3-cyclopropyl-7-fluoro-6-methoxyquinoxaline and 2-chloro-3-cyclopropyl-6-fluoro-7-methoxyquinoxaline

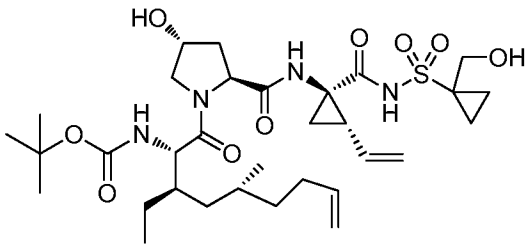
A solution of mixture of 3-cyclopropyl-7-fluoro-6-methoxyquinoxalin-2-ol and 3-cyclopropyl-6-fluoro-7-methoxyquinoxalin-2-ol (1.0 g, 4.27 mmol) in $POCl_3$ (10 mL, 107 mmol) was heated at 110 °C for 12 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ice cold water (200 mL). The aqueous solution was basified to PH ~9 using aqueous 10 % sodium bicarbonate solution, then was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine solution (100 mL); dried over

anhydrous sodium sulphate; filtered; then concentrated under reduced pressure to get the crude compound. The crude compound was purified by supercritical fluid chromatography ("SFC") to get 2-chloro-3-cyclopropyl-7-fluoro-6-methoxyquinoxaline (0.080 g, 0.317 mmol, 7.42%) and 2-chloro-3-cyclopropyl-6-fluoro-7-methoxyquinoxaline (0.110 g, 0.435 mmol, 10.20%). Bothe the compounds were confirmed by single crystal X- ray analysis.

2-chloro-3-cyclopropyl-7-fluoro-6-methoxyquinoxaline: ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.58 (s, 1 H) 7.31 (s, 1 H) 4.02 (s, 3 H) 2.68 (m, 1 H) 1.24 (m, 4 H). MS: MS *m/z* 253.1 (M^++1).

2-chloro-3-cyclopropyl-6-fluoro-7-methoxyquinoxaline: ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.56 (s, 1 H) 7.34 (s, 1 H) 4.01 (s, 3 H) 2.66 (m, 1 H) 1.24 (m, 4 H). MS: MS *m/z* 253.1 (M^++1).

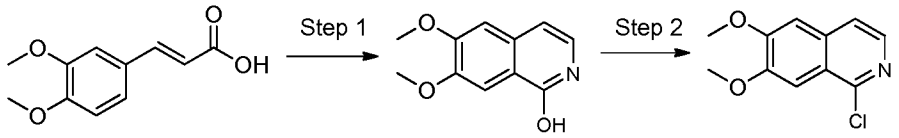
Preparation of tert-butyl ((2S,3R)-3-ethyl-1-((2S,4R)-4-hydroxy-2-(((1R,2S)-1-(((1-(hydroxymethyl)cyclopropyl)sulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)pyrrolidin-1-yl)-5-methyl-1-oxonon-8-en-2-yl)carbamate



To a stirred solution of (2S,4R)-1-((2S,3R)-2-((tert-butoxycarbonyl)amino)-3-ethyl-5-methylnon-8-enoyl)-4-hydroxypyrrolidine-2-carboxylic acid (1, 2.344 mmol) and (1R,2S)-1-amino-N-((1-(hydroxymethyl)cyclopropyl)sulfonyl)-2-vinylcyclopropanecarboxamide p-toluenesulfonic acid salt (1.115 g, 2.58 mmol) in CH_2Cl_2 (30 mL) and under nitrogen atmosphere was added HATU (0.891 g, 2.344 mmol) followed by DIPEA (1.228 mL, 7.03 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (250 mL) and washed with aq. HCl (1.5N); then washed with water. The organic layer was dried over anhydrous sodium sulfate; filtered; then concentrated under reduced pressure to afford a solid residue. This material was purified by silica gel chromatography using

6% MeOH in $CHCl_3$ as eluents to afford tert-butyl ((2S,3R)-3-ethyl-1-((2S,4R)-4-hydroxy-2-(((1R,2S)-1-(((1-(hydroxymethyl)cyclopropyl)sulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)pyrrolidin-1-yl)-5-methyl-1-oxonon-8-en-2-yl)carbamate (0.20 g, 13% yield) as an oil. MS: MS *m/z* 669.8 (M^++1).

Preparation of intermediate 1-chloro-6,7-dimethoxyisoquinoline



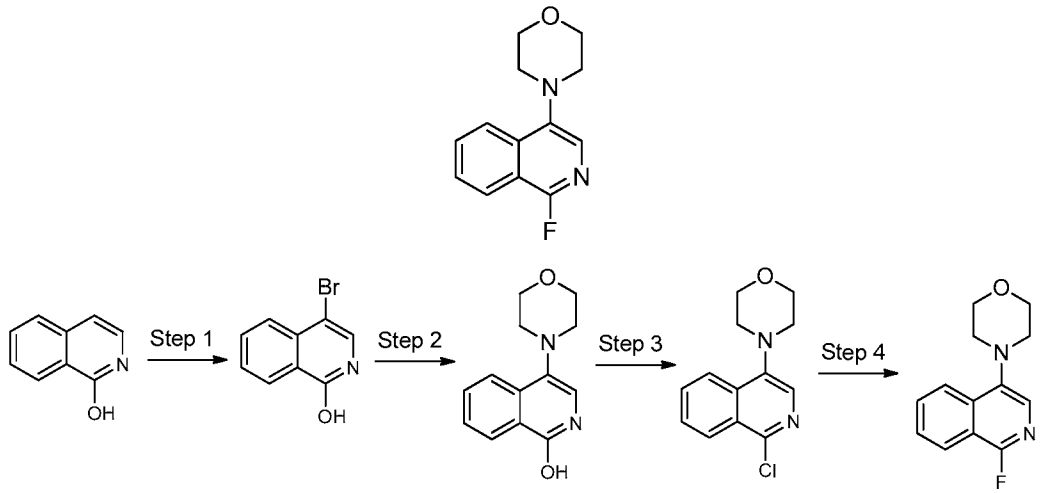
Step 1:

(E)-3-(3,4-dimethoxyphenyl)acrylic acid (2.08 g, 10 mmol), diphenylphosphoryl azide (2.75 g, 10 mmol), and Et_3N (1.1 g, 10 mmol) were dissolved in benzene and stirred for 1 h. The solution was concentrated under vacuum and the residue was purified by silica gel chromatography eluting with 20% EtOAc in hexanes to give 2 g of (E)-3-(3,4-dimethoxyphenyl)acryloyl azide as a yellow solid, which was taken into $PhCH_2Ph$ (8 mL). The resulting solution was slowly heated to 80°C for 1h and then to reflux for 3h. After cooling to rt, the solid was collected washing with benzene to give 1.1 g of 6,7-dimethoxyisoquinolin-1-ol.

Step 2:

A solution of 6,7-dimethoxyisoquinolin-1-ol (1 g) in $POCl_3$ (8 mL) was refluxed for 3 h. After concentration, the residue was taken into the mixture of DCM and 4N NaOH solution. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using 20% EtOAc/Hexanes as eluent to give 700 mg of the desired product 1-chloro-6,7-dimethoxyisoquinoline.

Preparation of intermediate 4-(1-fluoroisoquinolin-4-yl)morpholine



Step 1:

A mixture of 4-bromoisoquinolin-1-ol (7 g, 31.2 mmol) and NBS (6.74 g, 37.9 mmol) in acetonitrile (50 mL) was refluxed for 2h. After most of the solvent was removed, the mixture was taken into water. The solid was collected through a filter washing with water to give 7 g of a crude product 4-morpholinoisoquinolin-1-ol that was used in the next step as it is. MS: MS *m/z* 223.96 (M^++1).

Step 2:

A solution of 4-morpholinoisoquinolin-1-ol (1 g, 4.34 mmol) and morpholine (1.167 g, 13.39 mmol) in DMSO (5 mL) was heated to 145 °C for 6h. The reaction was diluted with ethyl acteate and washed with water, and brine. The organic phase was collected, dried over sodium sulfate, and concentrated under vacuum to give 1 g of the crude product 4-morpholinoisoquinolin-1-ol which was used in the next step as it is. MS: MS *m/z* 231.09 (M^++1).

Step 3:

A solution of 4-morpholinoisoquinolin-1-ol (1g, 4.34 mmol) in $POCl_3$ (5 mL, 53.6 mmol) was refluxed for 2 h. After concentration, the residue was taken into the mixture of DCM and 4N NaOH solution. The organic phase was collected and dried over sodium sulfate, filtered, then concentrated under vacuum. The crude material was purified by silica gel chromatography using 20% EtOAc/Hexanes as eluent to give 400 mg of the desired product 4-(1-chloroisoquinolin-4-yl)morpholine as a solid. ^{1}H NMR (400MHz, CHLOROFORM-d) 8.37 - 8.33 (m, 1H), 8.19 - 8.15 (m, 1H),

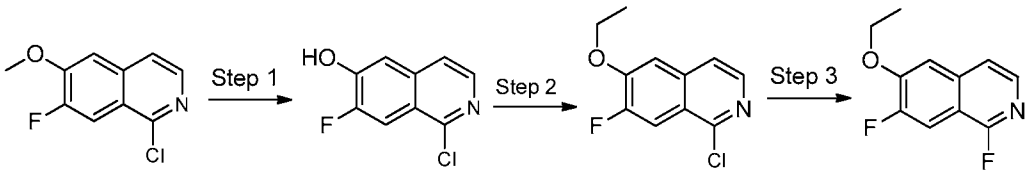
7.97 (s, 1H), 7.79 (ddd, *J*=8.3, 7.0, 1.3 Hz, 1H), 7.74 - 7.69 (m, 1H), 4.04 - 3.98 (m, 4H), 3.24 - 3.16 (m, 4H). MS: MS *m/z* 249.05 (M^++1).

Step 4:

To a solution of 4-(1-chloroisoquinolin-4-yl)morpholine (373 mg, 1.5 mmol) in DMSO (5 mL) was added CsF (456 mg, 3.00 mmol) and heated to 140 °C for 4 h. The reaction was diluted with ethylacteate and washed with water, and brine. The organic phase was collected, dried over sodium sulfate, and concentrated under vacuum to give the crude product which was purified by silica gel chromatography using a gradient of 5-25% EtOAc in hexanes. The product fractions were collected and the solvent removed under vacuum to give 0.28 g of the desired product 4-(1-fluoroisoquinolin-4-yl)morpholine. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.21 - 8.12 (m, 2H), 7.81 (ddd, *J*=8.4, 7.0, 1.1 Hz, 1H), 7.71 (d, *J*=1.8 Hz, 1H), 7.71 - 7.65 (m, 1H), 4.05 - 3.96 (m, 4H), 3.21 - 3.10 (m, 4H). MS: MS *m/z* 233.09 (M^++1).

Preparation of intermediate 6-ethoxy-1,7-difluoroisoquinoline





Step 1:

To a solution of 1-chloro-7-fluoro-6-methoxyisoquinoline (1.7 g, 8.03 mmol) in CH_2Cl_2 (5 mL) at room temperature was added BBr_3 (24.10 mL, 24.10 mmol) via syringe. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was cooled to -78°C and quenched with 1 ml of MeOH. After concentration, the residue was taken into water, the solid was collected washing with water to give 500 mg of the desired product 1-chloro-7-fluoroisoquinolin-6-ol.

Step 2:

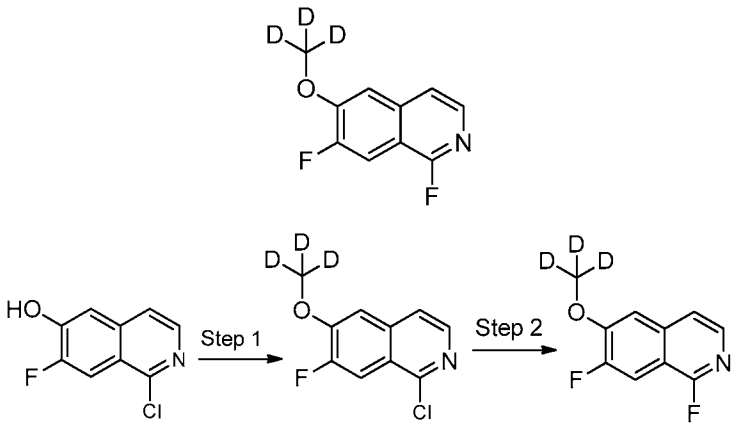
A mixture of 1-chloro-7-fluoroisoquinolin-6-ol (1.186 g, 6 mmol), bromoethane (1.308 g, 12.00 mmol), and K_2CO_3 (2.488 g, 18.00 mmol) in acetone (20 mL) was refluxed for 16 h. After filtration washing with acetone, the filtrate was

concentrated and purified by Silica gel chromatography eluting with 10-20% ethyl acetate in hexane to give 1.1 g of the product 1-chloro-6-ethoxy-7-fluoroisoquinoline as a solid. MS: MS *m/z* 226.03 (M^++1).

Step 3:

To a solution of 1-chloro-6-ethoxy-7-fluoroisoquinoline (1.128 g, 5 mmol) in DMSO (10 mL) was added CsF (1.519 g, 10.00 mmol) and heated to 140 °C for 4 hrs. The reaction was diluted with ethylacteate and washed with water, and brine. The organic phase was collected, dried over sodium sulfate, and concentrated under vacuum to give the crude product which was purified by silica gel chromatography using a gradient of 5-25% EtOAc in hexanes. The product fractions were collected and the solvent removed under vacuum to give 1.1 g of the desired product 6-ethoxy-1,7-difluoroisoquinoline. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.00 (d, *J*=5.5 Hz, 1H), 7.77 (dd, *J*=10.8, 0.5 Hz, 1H), 7.41 (dd, *J*=5.8, 1.3 Hz, 1H), 7.21 (dd, *J*=7.8, 1.8 Hz, 1H), 4.28 (q, *J*=7.0 Hz, 2H), 1.59 (t, *J*=7.0 Hz, 3H). MS: MS *m/z* 210.03 (M^++1).

Preparation of intermediate 1,7-difluoro-6-(D_3-methoxy)isoquinoline



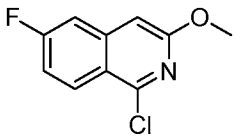
Step 1:

A mixture of 1-chloro-7-fluoroisoquinolin-6-ol (0.198 g, 1 mmol), CD_3I (0.290 g, 2.000 mmol), and K_2CO_3 (0.415 g, 3.00 mmol) in acetone (20 mL) was refluxed for 16 h. After filtration washing with acetone, the filtrate was concentrated and purified by Silica gel chromatography eluting with 10-20% ethyl acetate in hexane to give 0.16 g of the product as a solid. MS: MS *m/z* 215.09 (M^++1).

Step 2:

To a solution of 1-chloro-7-fluoro-6-(D_3-methoxy)isoquinoline (172 mg, 0.8 mmol) in DMSO (5 mL) was added CsF (243 mg, 1.600 mmol) and heated to 140 °C for 4 h. The reaction was diluted with ethylacteate and washed with water, and brine. The organic phase was collected, dried over sodium sulfate, and concentrated under vacuum to give the crude product which was purified by silica gel chromatography using a gradient of 5-25% EtOAc in hexanes. The product fractions were collected and the solvent removed under vacuum to give 0.14 g of the desired product 1,7-difluoro-6-(D_3-methoxy)isoquinoline. MS: MS *m/z* 199.09 (M^++1).

Preparation of 1-chloro-6-fluoro-3-methoxyisoquinoline

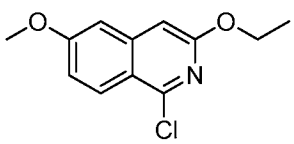


The intermediate 1-chloro-6-fluoro-3-methoxyisoquinoline was prepared by following the procedure described herein for the preparation of intermediate 5-chloro-1-fluoro-3-isopropoxyisoquinoline except that 1-chloro-6-fluoroisoquinolin-3-ol was used instead of 1,5-dichloroisoquinolin-3-ol and iodomethane was used instead of 2-bromopropane in step 1.

Step 1:

Modifications: 920 mg 1-chloro-6-fluoroisoquinolin-3-ol used, 800 mg product 1-chloro-6-fluoro-3-methoxyisoquinoline was obtained (81% yield); MS: MS *m/z* 212.0 (M^++1).

Preparation of 1-chloro-3-ethoxy-6-methoxyisoquinoline

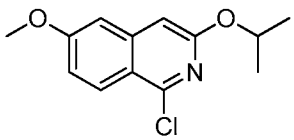


The intermediate 1-chloro-3-ethoxy-6-methoxyisoquinoline was prepared by following the procedure described herein for the preparation of intermediate 5-chloro-1-fluoro-3-isopropoxyisoquinoline except that 1-chloro-6-methoxyisoquinolin-3-ol was used instead of 1,5-dichloroisoquinolin-3-ol and iodoethane was used instead of 2-bromopropane in step 1.

Step 1:

Modifications: 800 mg 1-chloro-6-methoxyisoquinolin-3-ol used, 500 mg product 1-chloro-3-ethoxy-6-methoxyisoquinoline was obtained (55% yield); MS: MS *m/z* 238.0 (M^++1).

Preparation of 1-chloro-3-isopropoxy-6-methoxyisoquinoline

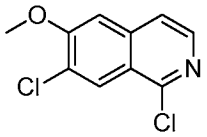


The intermediate 1-chloro-3-isopropoxy-6-methoxyisoquinoline was prepared by following the procedure described herein for the preparation of intermediate 5-chloro-1-fluoro-3-isopropoxyisoquinoline except that 1-chloro-6-methoxyisoquinolin-3-ol was used instead of 1,5-dichloroisoquinolin-3-ol in step 1.

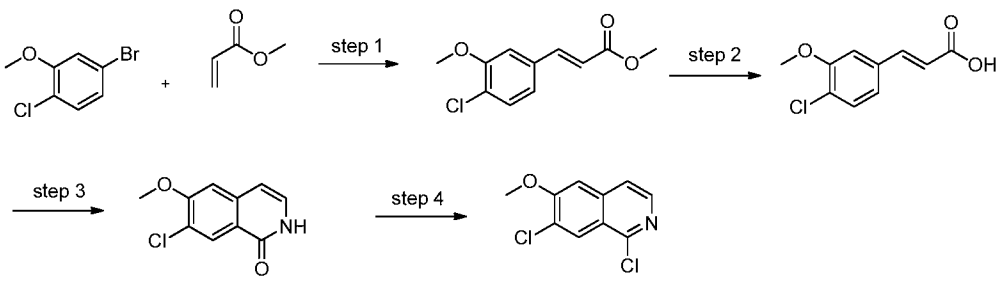
Step 1:

Modifications: 800 mg 1-chloro-6-methoxyisoquinolin-3-ol used, 200 mg product 1-chloro-3-isopropoxy-6-methoxyisoquinoline was obtained (21% yield); MS: MS *m/z* 252.0 (M^++1).

Preparation of 1,7-dichloro-6-methoxyisoquinoline



Scheme



Step 1:

To a mixture of $Pd_2(dba)_3$ (0.379 g, 0.414 mmol) and 4-bromo-1-chloro-2-methoxybenzene (3.67 g, 16.57 mmol) was added N-cyclohexyl-N-methylcyclohexanamine (3.56 g, 18.23 mmol), tert-Bu_3P (0.168 g, 0.829 mmol) in

1ml of dioxane. Stirred for 5 mins before addition of methyl acrylate (2.85 g, 33.1 mmol) and 20ml of dioxane. The mixture was stirred for 16 h at RT. The mixture was concentrated and purified by silica gel chromatography using 15% EtOAc/hexane to give 2.0 g (53%) (E)-methyl 3-(4-chloro-3-methoxyphenyl)acrylate as a white solid.

Step 2:

A mixture of (E)-methyl 3-(4-chloro-3-methoxyphenyl)acrylate (2 g, 8.82 mmol) and NaOH (0.706 g, 17.65 mmol) in H_2O/MeOH(1:2) was refluxed at 60 °C for 1h. The reaction was diluted with EtOAc and water. The aqueous layer was collected and acidified with 1N HCl and extracted with EtOAc. The organic layer was collected and dried over sodium sulfate, filtered and concentrated under vacuum to give 1.29 g (69%) (E)-3-(4-chloro-3-methoxyphenyl)acrylic acid as a light yellow solid.; ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.62 (d, *J*=16.1 Hz, 1H), 7.36 (d, *J*=8.1 Hz, 1H), 7.27 (d, *J*=1.8 Hz, 1H), 7.14 (dd, *J*=8.2, 1.9 Hz, 1H), 6.50 (d, *J*=16.1 Hz, 1H), 3.91 (s, 3H); MS: MS *m/z* 211.2 (M^--1).

Step 3:

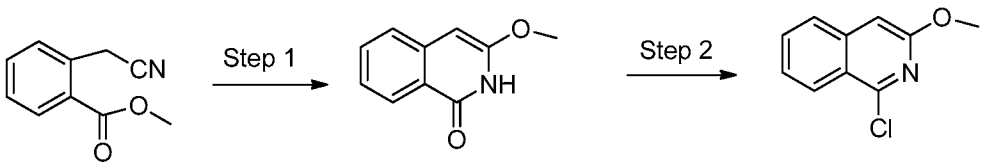
To a solution of (E)-3-(4-chloro-3-methoxyphenyl)acrylic acid (1.29 g, 6.07 mmol) and triethylamine (1.624 mL, 11.56 mmol) in Benzene (50 mL) was added diphenyl phosphorazidate (1.252 mL, 5.78 mmol). After stirring for 3h, the reaction was concentrated and then purified by Silica gel chromatography eluting with 20% Ethyl acetate in hexanes to give 1.15 g (E)-3-(4-chloro-3-methoxyphenyl)acryloyl azide as a light yellow solid. (E)-3-(4-chloro-3-methoxyphenyl)acryloyl azide (1.15 g, 4.84 mmol) was then suspended in diphenylmethane (10 mL) and was slowly heated to 80°C for 1h and then to reflux for 4h. After cooling to RT for 16 h, the solid that formed was collected and washed with benzene to give 1.14 g (83%) 7-chloro-6-methoxyisoquinolin-1(2H)-one as a solid. ^{1}H NMR (400MHz, METHANOL-d_4) δ 8.21 (s, 1H), 7.21 (s, 1H), 7.14 (d, *J*=7.3 Hz, 1H), 6.63 (d, *J*=7.3 Hz, 1H), 3.99 (s, 3H); MS: MS *m/z* 210.1 (M^++1).

Step 4:

A solution of 7-chloro-6-methoxyisoquinolin-1(2H)-one in 7 ml of $POCl_3$ was refluxed for 4 h. The solvent was removed under vacuum. The residue was taken into the mixture of DCM and 4N NaOH solution and adjusted PH to 7. The organic layer

was separated and washed with brine. The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica gel chromatography using 30% EtOAc/Hexane. The product fractions were collected and the solvent removed under vacuum to give 400mg (92%) 1,7-dichloro-6-methoxyisoquinoline as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.37 (s, 1H), 8.24 (d, *J*=5.5 Hz, 1H), 7.51 (d, *J*=5.5 Hz, 1H), 7.16 (s, 1H), 4.08 (s, 3H); MS: MS *m/z* 228.0 (M^++1).

Preparation of 1-chloro-3-methoxyisoquinoline



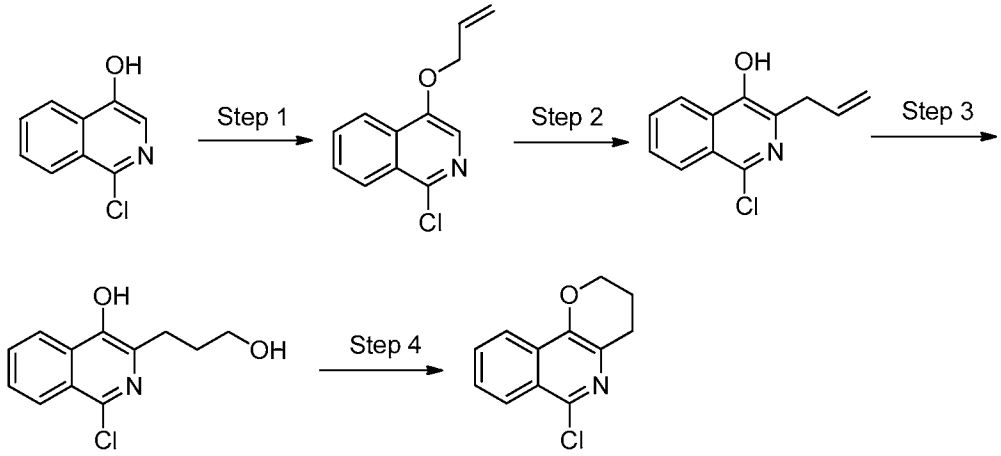
Step 1:

A mixture of methyl 2-(cyanomethyl)benzoate (3.50 g, 20 mmol) and sodium methoxide (10 mL, 25% wt in methanol) in 35 mL MeOH was heated to reflux under nitrogen for 3 h. While still hot, the solution was acidified with 1N HCl solution until the green solution turned to yellow color and a lot of white solid precipitated out. After cooling, the precipitated product was collected by filtration, washed with water and dried to yield the desired product 3-methoxyisoquinolin-1(2H)-one as a white solid (2.8 g, 80%). MS: MS *m/z* 176.1 (M^++1).

Step 2:

3-methoxyisoquinolin-1(2H)-one (2.8 g, 16.0 mmol) in $POCl_3$ (10 mL) was heated to reflux for 3 h then evaporated *in vacuo*. The residue was poured into iced $NaHCO_3$ solution (50 mL). The product was extracted with EtOAc for 2 times. The organic layer was washed with brine, dried over $MgSO_4$, filtered, evaporated. The residue was purified by flash chromatography with 20% then 40% of EtOAc/ hexane to afford 1.36 g (44%) of the desired product 1-chloro-3-methoxyisoquinoline as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) 8.29 - 8.16 (d, *J*=8.3 Hz, 1H), 7.72 (d, *J*=8.3 Hz, 1H), 7.63 (ddd, *J*=8.3, 6.8, 1.1 Hz, 1H), 7.47 (ddd, *J*=8.5, 7.0, 1.1 Hz, 1H), 6.98 (s, 1H), 4.05 (s, 3H). MS: MS *m/z* 194.0 (M^++1).

Preparation of 6-chloro-3,4-dihydro-2H-pyrano[3,2-c]isoquinoline



Step 1:

To a stirring solution of NaH (0.334 g, 8.35 mmol) in DMF (10 mL) at 0°C was added 1-chloroisoquinolin-4-ol (1 g, 5.57 mmol). The mixture was stirred at 0°C for 10 mins before the addition of allyl bromide (0.808 g, 6.68 mmol) dropwise. The reaction mixture was stirred at rt for 1h. The reaction mixture was diluted with ethyl acetate and then quenched with 1N HCl solution. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to get the crude material. The material was purified by flash chromatography with 20% of EtOAc/ hexane to afford 4-(allyloxy)-1-chloroisoquinoline (1.0 g, 4.55 mmol, 83 % yield) as a white solid. MS: MS *m/z* 220.1 (M^++1).

Step 2:

4-(allyloxy)-1-chloroisoquinoline (1.0 g, 4.55 mmol) was dissolved in diglyme (5 mL) and heated to 180°C for 1h. The reaction was cooled down to rt before adding EtOAc and water. Washed EtOAc layer with water then brine solution. The organic layer was then dried and concentrated. The residue was purified by flash chromatography with 20% of EtOAc/ hexane to afford 3-allyl-1-chloroisoquinolin-4-ol (670 mg, 67%) as product. MS: MS *m/z* 220.1 (M^++1).

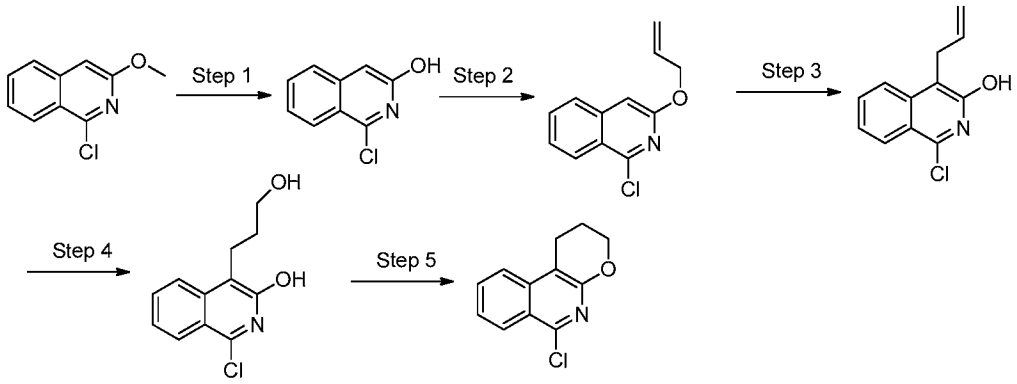
Step 3:

To a stirred solution of 3-allyl-1-chloroisoquinolin-4-ol (670 mg, 3.05 mmol) in dry tetrahydrofuran (5 mL) at room temperature was added 0.5 M in THF solution of 9-BBN (18.30 mL, 9.15 mmol) and the mixture was stirred for overnight. 3N NaOH (9.15 mL, 27.5 mmol) and H_2O_2 (2.83 mL, 30.5 mmol) were the added to the mixture. The mixture was stirred for 45 min before quenching with sat.NaCl solution. 1 N HCl was then added to the solution to adjust PH<7. The reaction was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated to afford a yellow oil that was chromatographed using 20-40%EtOAc/hexane to obtain 1-chloro-3-(3-hydroxypropyl)isoquinolin-4-ol (520mg , 70%) as product. MS: MS *m/z* 238.0 (M^++1).

Step 4:

To a solution of triphenylphosphine (1.03 g, 3.94 mmol) and 1-chloro-3-(3-hydroxypropyl)isoquinolin-4-ol (520 mg, 2.18 mmol) in THF (2 mL) at 0°C was added diisopropyl azodicarboxylate (0.85 mL, 4.38 mmol) dropwise. The resulting solution was stirred for 4 h at rt. After concentration of solvent, the residue was purified by silica gel chromatography eluting with 0%-20% ethyl acetate in hexane to give the desired product 6-chloro-3,4-dihydro-2H-pyrano[3,2-c]isoquinoline (350 mg, 73%) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) 8.27 - 8.20 (m, 1H), 8.13 (d, *J*=8.3 Hz, 1H), 7.73 (ddd, *J*=8.2, 6.8, 1.3 Hz, 1H), 7.67 - 7.60 (m, 1H), 4.45 - 4.31 (m, 2H), 3.07 (t, *J*=6.5 Hz, 2H), 2.29 - 2.15 (m, 2H); MS: MS *m/z* 220.0 (M^++1).

Preparation of 6-chloro-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline



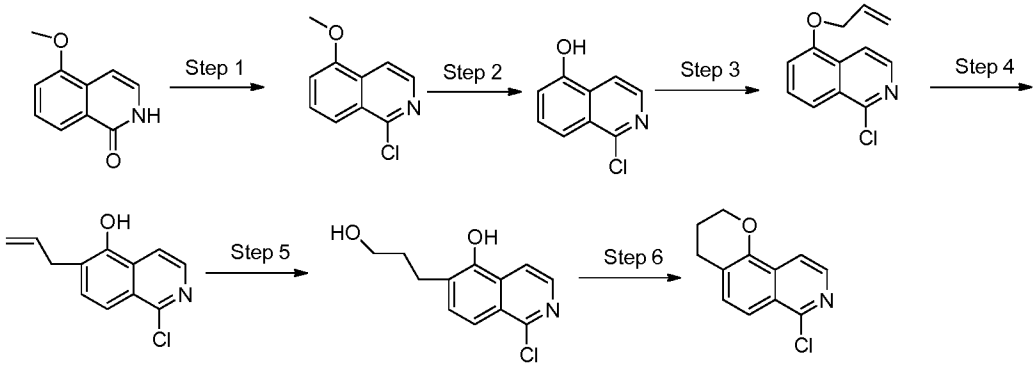
Step 1:

Dissolve 1-chloro-3-methoxyisoquinoline (370 mg, 1.911 mmol) in DCM (5 mL) and cool down the solution to -78°C. 1M BBr_3 (7.64 mL, 7.64 mmol) in DCM solution was then added to the reaction. The reaction was warmed up to rt slowly and run for 5h. Cool down the reaction mixture to -78°C and quench with 1N NaOH until PH=7. The product was extracted with EtOAc. EtOAc layer was washed with brine, dried and concentrated. The crude material 1-chloroisoquinolin-3-ol (328 mg, 96%) was used directly for the next step reaction. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.23 (d, *J*=9.5 Hz, 1H), 7.73 (d, *J*=8.5 Hz, 1H), 7.66 (ddd, *J*=8.3, 6.8, 1.1 Hz, 1H), 7.47 (ddd, *J*=8.4, 6.9, 1.3 Hz, 1H), 7.04 (s, 1H).

Steps 2-5:

6-chloro-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline was then prepared using the similar procedure described for synthesizing 6-chloro-3,4-dihydro-2H-pyrano[3,2-c]isoquinoline. 1-chloroisoquinolin-3-ol was used as starting material in step 2 instead of 1-chloroisoquinolin-4-ol. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.25 (dd, *J*=17.3, 8.3 Hz, 1H), 7.84 - 7.76 (m, 1H), 7.74 - 7.68 (m, 1H), 7.56 - 7.46 (m, 1H), 4.42 (dd, *J*=5.6, 4.9 Hz, 2H), 3.05 (q, *J*=6.4 Hz, 2H), 2.27 - 2.03 (m, 2H). MS: MS *m/z* 220.0 (M^++1).

Preparation of 7-chloro-3,4-dihydro-2H-pyrano[2,3-f]isoquinoline



Step 1:

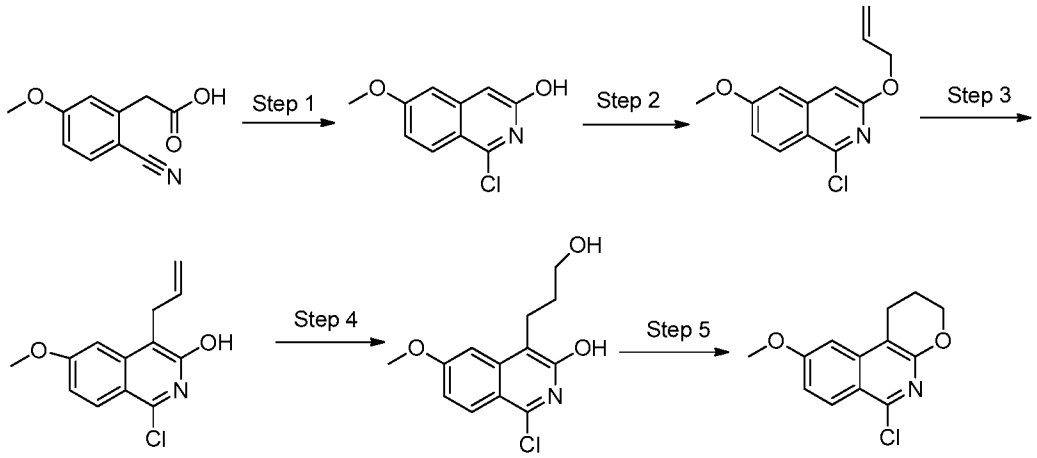
A solution of 5-methoxyisoquinolin-1(2H)-one (0.76 g, 0.34 mmol) in $POCl_3$ (10 ml) was refluxed for 3h. The solvent was evaporated under reduced pressure and the residue was diluted with cold water. The aqueous solution was basified by solid sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel chromatography (20% ethyl acetate in pet ether) to get desired compound 1-chloro-5-methoxyisoquinoline (0.84 g, 100%) as white solid.

Steps 2-6:

7-chloro-3,4-dihydro-2H-pyrano[2,3-f]isoquinoline was then prepared using the similar procedure described for synthesizing 6-chloro-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline. 1-chloro-5-methoxyisoquinoline was used as starting material in step 2 instead of 1-chloro-3-methoxyisoquinoline.

^{1}H NMR (400MHz, METHANOL-d_4) δ 8.17 (d, *J*=5.8 Hz, 1H), 7.97 (dd, *J*=5.8, 0.8 Hz, 1H), 7.79 (d, *J*=8.8 Hz, 1H), 7.47 (d, *J*=8.8 Hz, 1H), 4.47 - 4.34 (m, 2H), 2.99 (t, *J*=6.4 Hz, 2H), 2.24 - 2.08 (m, 2H). MS: MS *m/z* 220.0 (M^++1).

Preparation of 6-chloro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline



Step 1:

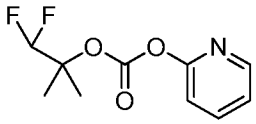
2-(2-cyano-5-methoxyphenyl)acetic acid (3.8 g, 19.88 mmol), and $SOCl_2$ (20 mL, 274 mmol) were stirred in dichloromethane (25 mL) at RT. The suspension became a solution over 8 h. The reaction was stirred overnight. The volatile organics were removed under vacuum and the residue was taken up in DCM and filtered. The filtrate was concentrated and then dissolved in 4 N HCl in dioxane (30 mL) and transferred to a sealed vessel and heated to 60 °C for 3 h. The reaction was cooled and the solid was collected, washed with dioxane, and dried under vacuum to give the product 1-chloro-6-methoxyisoquinolin-3-ol(3.3g, 70% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.10 (d, *J*=9.6 Hz, 1H), 7.12 (dd, *J*=9.3, 2.5 Hz, 1H), 6.95 (s, 2H), 3.98 (s, 3H).

Steps 2-5:

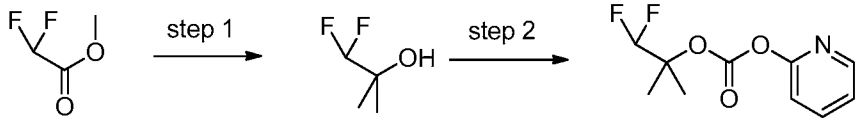
6-chloro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline was then prepared using the similar procedure described for synthesizing 6-chloro-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline. 1-chloro-6-methoxyisoquinolin-3-ol was used as starting material in step 2 instead of 1-chloroisoquinolin-3-ol.

^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.16 (d, *J*=9.0 Hz, 1H), 7.10 (dd, *J*=9.3, 2.3 Hz, 1H), 6.96 (d, *J*=2.3 Hz, 1H), 4.46 - 4.29 (m, 2H), 3.98 (s, 3H), 2.97 (t, *J*=6.5 Hz, 2H), 2.19 (dd, *J*=5.9, 4.6 Hz, 2H), MS: MS *m/z* 250.0 (M^++1).

Preparation of 1,1-difluoro-2-methylpropan-2-yl pyridin-2-yl carbonate



Scheme:



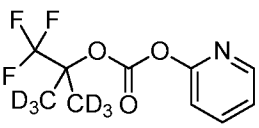
Step 1:

Methylmagnesium bromide (2.53 mL, 7.60 mmol) was added dropwise via syringe to a solution of methyl 2,2-difluoroacetate (0.398 g, 3.62 mmol) in Diethyl ether (10 mL) at -20 °C and stirred at this temp for 1 hr before warming up to RT. The reaction was quenched 4N HCl and extracted with a small portion of Et_2O. The organic layer was washed with brine, collected, dried over $MgSO_4$, filtered and concentrated to give a residue that was used in the next step as it was.

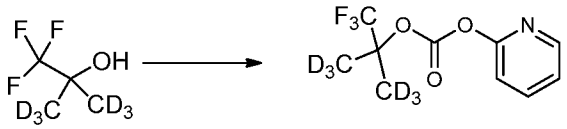
Step 2:

To a suspension of sodium hydride, 60% in mineral oil (0.145 g, 3.62 mmol) in THF (50 mL) was added 1,1-difluoro-2-methylpropan-2-ol (0.399 g, 3.62 mmol) in THF (1 mL) from Step 1 at 0°C. After stirring 30 min, to the solution was added with a solution of di(pyridin-2-yl) carbonate (0.783 g, 3.62 mmol) in THF (50 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. The reaction was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, concentrated to give a residue that was purified by silica gel chromatography eluting with 20% EtOAc in hexanes to afford 400 mg of the desired product 1,1-difluoro-2-methylpropan-2-yl pyridin-2-yl carbonate as an oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.47 - 8.39 (m, 1H), 7.91 - 7.74 (m, 1H), 7.32 - 7.23 (m, 1H), 7.14 (dt, *J*=8.2, 0.8 Hz, 1H), 6.22 - 5.89 (m, 1H), 1.65 (t, *J*=1.5 Hz, 6H).

Preparation of pyridin-2-yl (1,1,1-trifluoro-D6-2-methylpropan-2-yl) carbonate

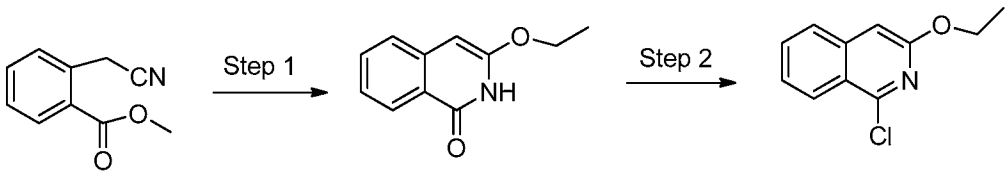


Scheme:



To a suspension of sodium hydride, 60% in mineral oil (686 mg, 17.16 mmol) in THF (10 mL) was added 1,1,1-trifluoro-D6-2-methylpropan-2-ol (2092 mg, 15.6 mmol) at 0ºC. After stirring 30 min, the solution was transferred to a solution of di(pyridin-2-yl) carbonate (3373 mg, 15.60 mmol) in THF (10 mL) through a cannula. The formed slurry was stirred at 0 °C for 30 min. The slurry was warmed to rt and stirred for 2 h. The reaction was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, concentrated to give a residue that was purified by Silica gel chromatography eluting with 20% EtOAc in hexanes to afford 800 mg of the desired product as an oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.43 (dd, *J*=4.9, 1.4 Hz, 1H), 7.88 - 7.79 (m, 1H), 7.32 - 7.25 (m, 1H), 7.14 (d, *J*=8.3 Hz, 1H).

Preparation of 1-chloro-3-ethoxyisoquinoline



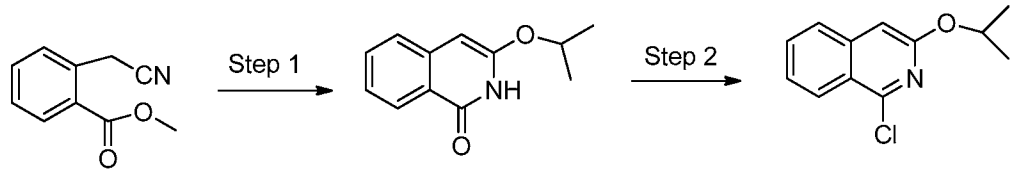
Step 1:

Na (1.18 g, 51.4 mmol) cut into small pieces and washed with hexane before adding to EtOH (40 mL) at r.t. The solution was heated to 80°C until all the Na disappeared. The reaction was cooled down to r.t then added methyl 2-(cyanomethyl)benzoate (3 g, 17.12 mmol). The mixture was heated to reflux under N_2 for 2 h. While still hot, the reaction was acidified with 1M HCl to adjust PH=7. The reaction was cooled down to r.t, filtered the solid and washed with H_2O. Dried under vacum to get 3-ethoxyisoquinolin-1(2H)-one (2.8 g, 86%) as an off-white solid. MS: MS *m/z* 190.1 (M^++1).

Step 2:

1-chloro-3-ethoxyisoquinoline was then prepared using the similar procedure described for synthesizing 1-chloro-3-methoxyisoquinoline. 3-ethoxyisoquinolin-1(2H)-one was used as starting material in step 2 instead of 3-methoxyisoquinolin-1(2H)-one. MS: MS *m/z* 208.1 (M^++1).

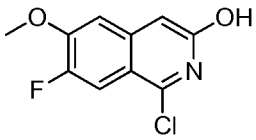
Preparation of 1-chloro-3-isopropoxyisoquinoline



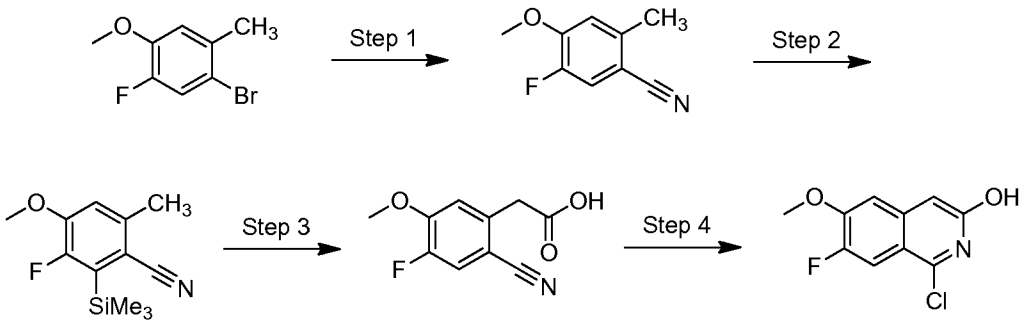
Step 1-2:

1-chloro-3-isopropoxyisoquinoline was prepared using the similar procedure described for synthesizing 1-chloro-3-ethoxyisoquinoline. Isopropyl alcohol was used as reagent in step 1 instead of ethanol. MS: MS *m/z* 222.1 (M^++1).

Preparation of 1-chloro-7-fluoro-6-methoxyisoquinolin-3-ol



Scheme:



Step 1:

To a Schlenk flask equipped with a stir bar was added $Pd(OAc)_2$ (0.307 g, 1.37 mmol) and 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl ("XPhos", 1.31 g, 2.74 mmol). The flask was sealed with a rubber septum and then the flask was thrice evacuated and placed under nitrogen atmosphere to establish a N_2 atmosphere. To the flask was added dry CH_2Cl_2 (1mL) and Et_3N (0.1 mL). The stirred solution was warmed with a heat gun until the solvent condensed on the walls of the flask. The solvent was removed under vacuum with the exclusion of oxygen. To the flask, while under positive nitrogen pressure, was added 1-bromo-5-fluoro-4-methoxy-2-methylbenzene (6.00 g, 27.4 mmol), Na_2CO_3 (0.363 g, 3.42 mmol), and potassium hexacyanoferrate(II) trihydrate (5.78 g, 13.7 mmol). The flask was thrice evacuated and placed under nitrogen atmosphere. To the flask was added water (20

mL) and acetonitrile (20 mL). The flask was placed in a 70 °C oil bath with stirring for 18 h. The mixture was cooled to room temperature, transferred to a separatory funnel, and then diluted with EtOAc and water. The mixture was shaken; the phases were separated. The organic phase was washed with water; then brine; dried over $MgSO_4$; filtered; and then concentrated in vacuo. The resulting residue was subjected to silica gel chromatography (hexanes:EtOAc, 95:5 to 50:50) to afford 5-fluoro-4-methoxy-2-methylbenzonitrile as a white solid (3.43 g, 76 %). ^{1}H-NMR (500MHz, DMSO-d_6) δ 7.73 (d, *J*=11.3 Hz, 1H), 7.28 (d, *J*=8.4 Hz, 1H), 3.91 (s, 3H), 2.45 (s, 3H).

Step 2:

To a round-bottom flask equipped with a stir bar was added THF (50 mL) and N,N-diisopropylamine (2.98 mL, 20.9 mmol). The solution was cooled -78°C and to the solution was added dropwise n-butyllithium in hexanes (8.36 mL, 20.9 mmol). The solution was stirred for 10 minutes. To the solution was added 5-fluoro-4-methoxy-2-methylbenzonitrile (3.45 g, 20.9 mmol) in THF (15 mL). The solution was stirred for 30 min. To the solution was added dropwise chlorotrimethylsilane (2.64 mL, 20.9 mmol). The solution was stirred for an 60 minutes at -78 °C and then was allowed to warm to room temperature with stirring for 30 minutes. To the solution was carefully added water (80 mL). The mixture was transferred to a separatory funnel and the phases were separated. The aqueous phase was extracted with EtOAc. The combined organics were washed with brine; dried over Na_2SO_4; filtered; then concentrated in vacuo to afford 3-fluoro-4-methoxy-6-methyl-2-(trimethylsilyl)benzonitrile as a yellow solid (4.01 g, 81%). ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.84 (d, *J*=8.3 Hz, 1H), 3.91 (s, 3H), 2.52 (s, 3H), 0.50 - 0.45 (m, 9H).

Step 3:

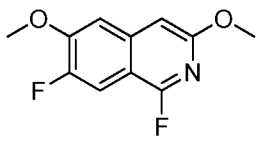
To a round-bottom flask equipped with a stir bar was added THF (85 mL) and *N,N*-diisopropylamine (2.65 mL, 18.6 mmol). The solution was cooled to -78 °C, then to the solution was added dropwise n-butyllithium in hexanes (7.43 mL, 18.58 mmol). The solution was stirred for 10 min. To the solution was added 3-fluoro-4-methoxy-6-methyl-2-(trimethylsilyl)benzonitrile (4.01 g, 16.9 mmol) in THF (5 mL). The solution was stirred for 30 min. Carbon dioxide gas was then bubbled through the solution until the solution became clear. To the solution was carefully added water (80 mL) and the resulting mixture was allowed to warmed to room temperature.

The mixture was transferred to a separatory funnel and was diluted with aq. NaOH (10 N, 40 mL). The mixture was twice washed with Et_2O. The aqueous phase was isolated, cooled in a 0 °C bath, and then acidified with concentrated aq. HCl. The resulting mixture was warmed to room temperature and then extracted with EtOAc. The organic phase was collected; dried over Na_2SO_4; filtered; then concentrated in vacuo to afford the 2-(2-cyano-4-fluoro-5-methoxyphenyl)acetic acid as a white solid (2.16 g, 61%). ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.37 (d, *J*=10.3 Hz, 1H), 6.98 (d, *J*=7.8 Hz, 1H), 3.96 (s, 3H), 3.89 (s, 2H).

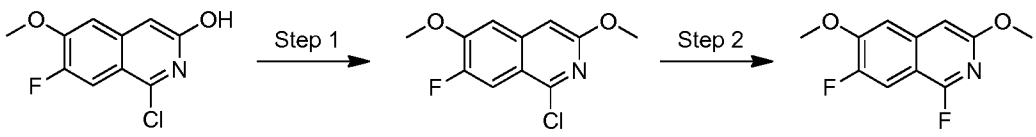
Step 4:

To a round-bottom flask equipped with a stir bar was added 2-(2-cyano-4-fluoro-5-methoxyphenyl)acetic acid (3.34 g, 16.0 mmol) and CH_2Cl_2. To the mixture was added $SOCl_2$ (5.00 mL, 68.5 mmol). The mixture was stirred at room temperatuer for 16 h to afford a homogeneous solution. The volatile organics were removed under vacuum and the residue was taken up in CH_2Cl_2 and filtered. The filtrate was concentrated in vacuo. The residue was dissolved in a solution of HCl in dioxane (4.0N, 30 mL) and then transfered to a bomb flask. The flask was sealed and then heated at 60 °C with stirring for 3 h. The mixture was cooled to room temperature and the solids were collected via filtration. The solids were washed with dioxane and then dried under vacuum to afford 1-chloro-7-fluoro-6-methoxyisoquinolin-3-ol as a colorless solid (1.83 g, 50%). ^{1}H-NMR (500MHz, DMSO-d_6) δ 7.76 (d, *J*=12.0 Hz, 1H), 7.44 (d, *J*=8.4 Hz, 1H), 6.92 (s, 1H), 3.98 (s, 3H).

Preparation of 1,7-difluoro-3,6-dimethoxyisoquinoline



Scheme:



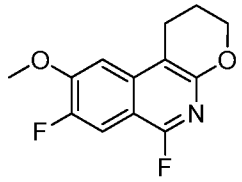
Step 1:

To a round-bottom flask equipped with a stir bar and charged with 1-chloro-7-fluoro-6-methoxyisoquinolin-3-ol (138 mg, 0.606 mmol) in DMF (5 mL) was added K_2CO_3 (168 mg, 1.21 mmol) and iodomethane (0.760 mL, 1.20 mmol). The mixture was stirred at room temperature for 16 h. To the solution was added K_2CO_3 (84 mg, 0.6 mmol) and iodomethane (0.38 mL, 0.6 mmol). The mixture was stirred at 40 °C for 2 h. The mixture was transferred to a separatory funnel and was diluted with water; then was extracted with EtOAc. The organic phase was washed with water; then brine; then dried over $MgSO_4$; filtered; then concentrated in vacuo. The resulting residue was subjected to silica gel chromatography (hexanes:EtOAc, 95:5 to 80:20) to afford 1-chloro-7-fluoro-3,6-dimethoxyisoquinoline as a white solid (100 mg, 68%). ^{1}H-NMR (500MHz, DMSO-d_6) δ 7.83 (dd, *J*=11.8, 0.5 Hz, 1H), 7.52 (d, *J*=8.4 Hz, 1H), 7.18 (s, 1H), 3.99 (s, 3H), 3.91 (s, 3H).

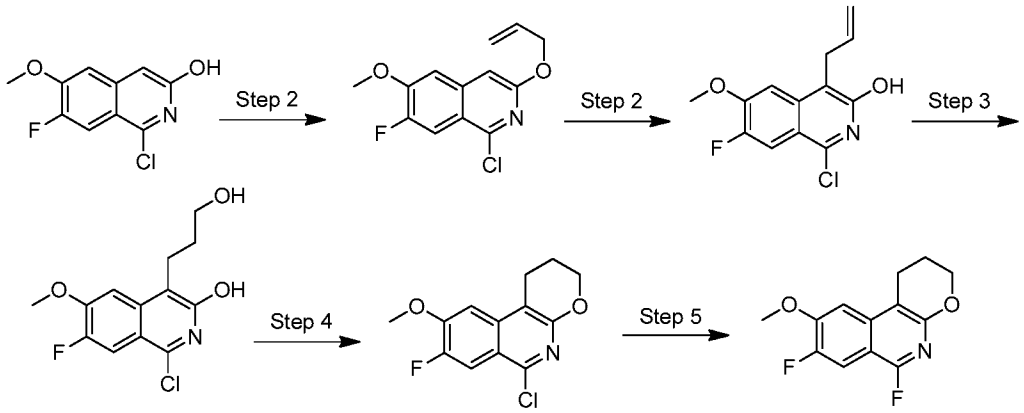
Step 2:

To a vial equipped with a stir bar was added 1-chloro-7-fluoro-3,6-dimethoxyisoquinoline (100 mg, 0.414 mmol), CsF (94 mg, 0.62 mmol) and DMSO (2 mL). The mixture was heated at 140 °C with stirring for 2 h. The mixture was transferred to a separatory funnel and was diluted with EtOAc. The mixture was washed with water; then brine. The organic phase was collected; dried over MgSO; filtered; then concentrated under vacuum. The resulting residue was subjected to silica gel chromatography (hexanes:EtOAc, 100:0 to 60:40) to afford 1,7-difluoro-3,6-dimethoxyisoquinoline as a yellow solid (80 mg, 86%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 7.64 (d, *J*=10.9 Hz, 1H), 7.04 (dd, *J*=7.8, 1.3 Hz, 1H), 6.79 (s, 1H), 4.04 (s, 3H), 4.00 - 3.98 (m, 3H).

Preparation of 6,8-difluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline



Scheme:



Step 1:

To a round-bottom flask equipped with a stir bar and placed under nitrogen atmosphere was added DMF (10 mL) and NaH (60% dispersion in oil, 55.0 mg, 1.38 mmol). The solution was cooled to 0 °C. To the solution was added 1-chloro-7-fluoro-6-methoxyisoquinolin-3-ol (285 mg, 1.25 mmol). The solution was stirred for 10 minutes. To the solution was added allylbromide (0.119 mL, 1.38 mmol). The solution was allowed to warm to room temperature with stirring for 1 h. The solution was transferred to a separatory funnel and was diluted with water; then extracted with EtOAc. The organic layer was washed with brine; dried over $MgSO_4$; filtered; and then concentrated in vacuo to afford 3-(allyloxy)-1-chloro-7-fluoro-6-methoxyisoquinoline as a solid (340 mg).

Step 2:

To a 2 dram vial equipped with a stir bar was added 3-(allyloxy)-1-chloro-7-fluoro-6-methoxyisoquinoline (all material from step 1, 340 mg, 1.27 mmol) and diethylene glycol dimethyl ether (5 mL). The vial was sealed with a PTFE-lined cap and then placed in a 175 °C heating block with stirring for 16 h. The solution was cooled to room temperature and then was transferred to a separatory funnel and diluted with water. The mixture was thrice extracted and EtOAc. The combined organics were washed with brine; dried over $MgSO_4$; filtered; then concentrated in vacuo to afford 4-allyl-1-chloro-7-fluoro-6-methoxyisoquinolin-3-ol as an orange-brown solid (306 mg, 90% over two steps). ^{1}H-NMR (500MHz, DMSO-d_6) δ 11.23

(s, 1H), 7.80 (d, *J*=11.8 Hz, 1H), 7.30 (d, *J*=8.4 Hz, 1H), 5.97 - 5.85 (m, 1H), 5.08 - 4.98 (m, 2H), 4.00 (s, 3H), 3.66 (d, *J*=6.1 Hz, 2H).

Step 3:

To a round-bottom flask equipped with a stir bar was added 4-allyl-1-chloro-7-fluoro-6-methoxyisoquinolin-3-ol (all material from step 2, 306 mg, 1.14 mmol) and THF (10 mL). To the solution was added 9-Borabicyclo[3.3.1]nonane ("9-BBN", 0.5M in THF, 6.86 mL, 3.43 mmol). The solution was stirred at room temperature until 1H-NMR analysis of a reaction aliquot indicated complete conversion of the alkene starting material. To the solution was added aq. NaOH (3.0 N, 3.43 mL, 10.3 mmol), then and aq. 30% H_2O_2 (1.17 mL, 11.4 mmol). The mixture was stirred for 16 h. To the mixture was acidified with via addition of aq. HCl (1.0 N). The mixture was transferred to a separatory funnel and was extracted with EtOAc. The organic phase was washed with brine; dried over $MgSO_4$; filtered; then concentrated in vacuo. The resulting residue was subjected to silica gel chromatography (hexanes:EtOAc, 80:20 to 50:50) to afford 1-chloro-7-fluoro-4-(3-hydroxypropyl)-6-methoxyisoquinolin-3-ol as a white solid (210 mg, 64%). ^{1}H-NMR (500MHz, acetone-d_6) δ 9.53 (br. s., 1H), 7.78 (d, *J*=12.0 Hz, 1H), 7.57 (d, *J*=8.2 Hz, 1H), 4.08 (s, 3H), 3.61 (br. s., 2H), 3.11 - 3.04 (m, 2H), 1.92 - 1.83 (m, 2H).

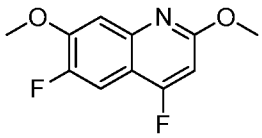
Step 4:

To a round-bottom flask equipped with a stir bar was added PPh_3 (347 mg, 1.32 mmol), 1-chloro-7-fluoro-4-(3-hydroxypropyl)-6-methoxyisoquinolin-3-ol (210 mg, 0.735 mmol), and THF (20 mL). The solution was cooled to 0 °C, then to the solution was added dropwise diisopropylazodicarboxylate ("DIAD", 0.286 mL, 1.47 mmol). The mixture was allowed to warm to room temperature with stirring for 4 h. The mixture was concentrated in vacuo and the resulting residue was subjected to silica gel purification to afford 6-chloro-8-fluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline as a yellow solid (171 mg). ^{1}H-NMR (500MHz, $CDCl_3$) δ 7.86 (d, *J*=11.7 Hz, 1H), 7.01 (d, *J*=7.9 Hz, 1H), 4.43 - 4.34 (m, 2H), 4.04 (s, 3H), 2.97 (t, *J*=6.5 Hz, 2H), 2.22 - 2.13 (m, 2H).

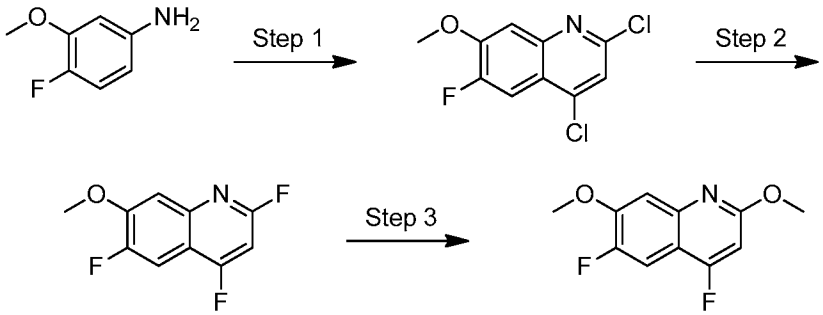
Step 5:

To a vial equipped with a stir bar was added 6-chloro-8-fluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline (all material from step 4, 171 mg, 0.639 mmol), CsF (146 mg, 0.958 mmol), and DMSO (3 mL). The vial was placed in a 140 °C heating block with stirring for 2 h. The mixture was transferred to a separatory funnel and was diluted with water. The mixture was extracted with EtOAc. The organic phase was washed with water; then brine; then dried over $MgSO_4$; filtered; then concentrated in vacuo. The resulting residue was subjected to silica gel chromatography (hexanes:EtOAc, 100:0 to 60:40) to afford 6,8-difluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline as a yellow solid (114 mg, 71% over two steps). MS: MS *m/z* 252.2 (M^++1).

Preparation of 4,6-difluoro-2,7-dimethoxyquinoline



Scheme:



Step 1:

To a large round-bottom flask equipped with a stir bar was added 4-fluoro-3-methoxyaniline (4.00 g, 28.3 mmol) and malonic acid (2.95 g, 28.3 mmol). To the flask was added $POCl_3$ (4.76 mL, 101 mmol). The flask was fitted with a bump-trap and then heated to 105 °C. After 5 minutes vigorous effervescence and foaming was observed. When the foaming had subsided, to the flask was added $POCl_3$ (4.76 mL, 101 mmol) upon which the mixture slowly became a homogeneous solution. The solution was stirred at 105 °C for 16 h. The solution was cooled to room temperature

and then concentrated in vacuo. The resulting oil residue was diluted with CH_2Cl_2 and to the mixture was added ice. Once the ice had melted, the flask was placed in a 0 °C bath and to the mixture was added aq. NaOH (10 N) to adjust the aq. phase to pH > 8. The mixture was transferred to a separatory funnel and the phases were separated. The organic phase was washed with brine; dried over $MgSO_4$; filtered; then concentrated in vacuo. The resulting residue was subjected to silica gel chromagraphy (hexanes:EtOAc, 95:5 to 80:20) to afford 2,4-dichloro-6-fluoro-7-methoxyquinoline as a white solid (3.7 g, 53%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 7.81 (d, *J*=11.3 Hz, 1H), 7.46 (d, *J*=7.9 Hz, 1H), 7.42 (s, 1H), 4.04 (s, 3H).

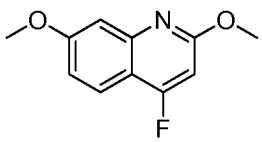
Step 2:

To a round-bottom flask equipped with a stir bar was added 2,4-dichloro-6-fluoro-7-methoxyquinoline (2.00 g, 8.13 mmol), CsF (3.09 g, 20.3 mmol) and DMSO (20 mL). The mixture was stirred at 140 °C for 2 h. The mixture was cooled to room temperature and then transferred to a separatory funnel; then diluted with water. The mixture was extracted with EtOAc. The organic phase was washed with water; then brine; dried over $MgSO_4$; filtered; then concentrated in vacuo to afford as a light-orange solid (1.75 g, 100%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 7.66 (d, *J*=10.7 Hz, 1H), 7.39 (dd, *J*=7.6, 1.5 Hz, 1H), 6.72 (dd, *J*=9.1, 1.5 Hz, 1H), 4.05 - 4.02 (m, 3H).

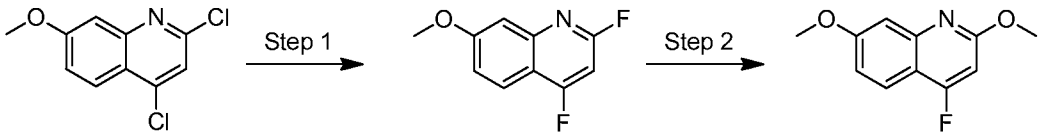
Step 3:

To a round-bottom flask equipped with a stir bar was added 2,4,6-trifluoro-7-methoxyquinoline (500 mg, 2.35 mmol) and THF (15 mL). To the solution was added NaOMe (25% in MeOH, 2.35 mmol). The solution was stirred at room temperature for 16 h. The solution was transferred to a separatory funnel and was diluted with EtOAc; then washed with brine. The organic solution was dried over $MgSO_4$; filtered; then concentrated in vacuo. The resulting residue was subjected to silica gel chromatography (hexanes:EtOAc. 95:5 to 80:20) to afford 4,6-difluoro-2,7-dimethoxyquinoline as a white solid (268 mg, 51%). NMR.

Preparation of 4-fluoro-2,7-dimethoxyquinoline



Scheme:



Step 1:

To a round-bottom flask equipped with a stir bar was added 2,4-dichloro-7-methoxyquinoline (905 mg, 3.97 mmol), CsF (1.51 g, 9.92 mmol) and DMSO (20 mL). The mixture was stirred at 140 °C for 2 h. The mixture was allowed to cool to room temperature; then was transferred to a separatory funnel and diluted with water. The mixture was extracted with EtOAc. The organic phase was dried over $MgSO_4$; filtered; then concentrated in vacuo to afford 2,4-difluoro-7-methoxyquinoline as a light-orange solid (706 mg, 91%). MS: MS *m/z* 196.2 (M^++1).

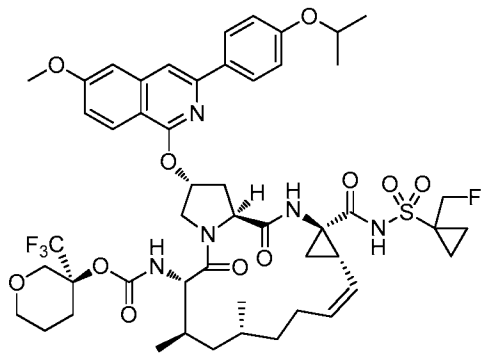
Step 2:

To a round-bottom flask equipped with a stir bar was added 2,4-difluoro-7-methoxyquinoline (all material from step 1, 706 mg, 3.62 mmol) and THF (15 mL). To the solution was added sodium methoxide (25% in methanol, 3.62 mmol). The solution was stirred at room temperature for 16 h. The solution was transferred to a separatory funnel and was diluted with EtOAc; then washed with brine. The organic phase was dried over $MgSO_4$; filtered; then concentrated in vacuo. The resulting residue was subjected to silica gel chromatography (hexanes:EtOAc, 95:5 to 80:20) to afford 4-fluoro-2,7-dimethoxyquinoline as a white solid (381 mg, 1.84 mmol, 51%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 7.83 (d, *J*=9.0 Hz, 1H), 7.22 (t, *J*=2.1 Hz, 1H), 7.05 (dd, *J*=9.0, 2.5 Hz, 1H), 6.45 (d, *J*=10.7 Hz, 1H), 4.06 (s, 3H), 3.96 - 3.92 (m, 3H); ^{13}C-NMR (101MHz, $CDCl_3$) δ 167.8, 165.2, 164.0 (d, *J*=14.6 Hz), 161.9, 149.8 (d, *J*=6.9 Hz), 121.7 (d, *J*=4.6 Hz), 116.4, 106.5, 106.4, 94.4 (d, *J*=19.3 Hz), 55.5, 53.7.

After the desired product was eluted from silica gel a second major product was isolated: 2-fluoro-4,7-dimethoxyquinoline as a white solid (222 mg, 30%). ^{1}H-

NMR (400MHz, $CDCl_3$) δ 8.00 (d, *J*=9.0 Hz, 1H), 7.20 (d, *J*=2.5 Hz, 1H), 7.09 (dd, *J*=9.0, 2.5 Hz, 1H), 6.26 (s, 1H), 4.06 - 4.02 (m, 3H), 3.92 (s, 3H); ^{13}C-NMR (101MHz, $CDCl_3$) δ 166.2 (d, *J*=13.1), 164.4, 162.0, 161.9, 147.9 (d, *J*=21.6 Hz), 123.2, 117.2 (d, *J*=2.3 Hz), 114.6, 106.8, 86.5 (d, *J*=47.0 Hz), 56.1, 55.5.

Preparation of Compound 1183



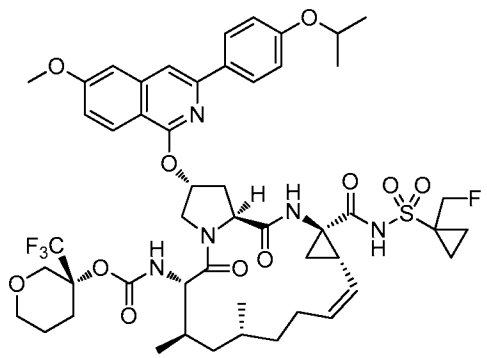
Compound 1183

Compound 1183 was prepared using 1-chloro-3-(4-isopropoxyphenyl)-6-methoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1183: (S)-3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, CD_3OD) δ 8.08 (d, J=8.9 Hz, 2H), 8.02 (d, J=8.9 Hz, 1H), 7.64 (s, 1H), 7.19 (d, J=2.1 Hz, 1H), 7.04 - 6.97 (m, 3H), 6.00 (br. s., 1H), 5.62 - 5.54 (m, 1H), 5.02 (br. s., 1H), 4.77 (d, J=11.3 Hz, 1H), 4.72 - 4.55 (m, 4H), 4.27 - 4.19 (m, 1H), 4.11 (dd, J=11.6, 3.7 Hz, 1H), 3.96 - 3.87 (m, 4H), 3.61 - 3.56 (m, 1H), 3.50 - 3.38 (m, 2H), 2.79 (dd, J=13.7, 7.0 Hz, 1H), 2.70 (br. s., 1H), 2.51 - 2.36 (m, 2H), 2.30 (d, J=14.0 Hz, 1H), 2.02 - 1.86 (m, 2H), 1.86 - 1.72 (m, 2H), 1.69 (dd, J=8.2, 5.5 Hz, 2H), 1.66 - 1.52 (m, 3H), 1.52 -

1.42 (m, 2H), 1.37 (s, 3H), 1.36 (s, 3H), 1.35 - 1.19 (m, 3H), 1.17 (br. s., 1H), 1.02 (t, J=6.9 Hz, 6H), 0.85 (t, J=12.1 Hz, 1H) ; MS: MS *m/z* 1016.6 (M^++1).

Preparation of Compound 1184

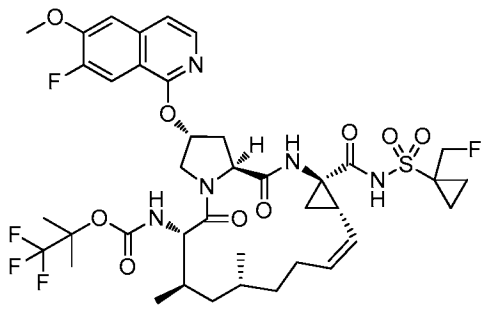


Compound 1184

Compounds 1184 was prepared using 1-chloro-3-(4-isopropoxyphenyl)-6-methoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1184: (R)-3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, CD_3OD) δ 8.07 (d, J=8.9 Hz, 2H), 8.01 (s, 1H), 7.63 (s, 1H), 7.17 (d, J=2.1 Hz, 1H), 7.03 - 6.98 (m, 3H), 5.97 (br. s., 1H), 5.52 - 5.44 (m, 1H), 4.84 (d, J=11.0 Hz, 1H), 4.79 - 4.64 (m, 3H), 4.64 - 4.48 (m, 2H), 4.25 (d, J=11.6 Hz, 1H), 4.10 (dd, J=11.6, 3.7 Hz, 1H), 3.98 (d, J=11.0 Hz, 1H), 3.95 - 3.90 (m, 3H), 3.73 - 3.67 (m, 1H), 3.55 (d, J=11.9 Hz, 1H), 3.52 - 3.43 (m, 1H), 2.83 (dd, J=13.9, 7.2 Hz, 1H), 2.67 (br. s., 1H), 2.50 - 2.33 (m, 3H), 1.95 - 1.72 (m, 5H), 1.70 - 1.46 (m, 5H), 1.44 - 1.38 (m, 1H), 1.36 (d, J=6.1 Hz, 6H), 1.35 - 1.24 (m, 1H), 1.24 - 1.07 (m, 3H), 1.02 (d, J=6.4 Hz, 3H), 0.98 (d, J=6.7 Hz, 3H), 0.84 (t, J=11.6 Hz, 1H) ; MS: MS *m/z* 1016.5 (M^++1).

Preparation of Compound 1185

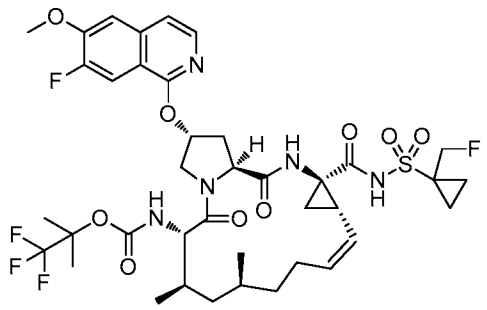


Compound 1185

Compounds 1185 was prepared using 1,7-difluoro-6-methoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1185: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.27 (s, 1H), 9.01 (s, 1H), 8.00 (d, J=5.8 Hz, 1H), 7.72 (d, J=11.6 Hz, 1H), 7.64 (d, J=7.6 Hz, 1H), 7.58 (d, J=8.5 Hz, 1H), 7.37 (d, J=5.8 Hz, 1H), 5.81 (br. s., 1H), 5.55 - 5.49 (m, 1H), 5.01 (t, J=9.9 Hz, 1H), 4.90 - 4.70 (m, J=11.3 Hz, 1H), 4.61 - 4.46 (m, 3H), 3.99 (s, 3H), 3.93 - 3.88 (m, 1H), 3.71 (dd, J=10.5, 8.1 Hz, 1H), 2.71 - 2.59 (m, 2H), 2.39 - 2.28 (m, 2H), 1.93 - 1.79 (m, 2H), 1.71 (dd, J=12.7, 6.3 Hz, 1H), 1.67 - 1.55 (m, 4H), 1.53 (d, J=5.5 Hz, 3H), 1.49 - 1.42 (m, 1H), 1.42 - 1.32 (m, 2H), 1.29 (s, 3H), 1.24 (d, J=15.0 Hz, 1H), 1.15 (d, J=12.8 Hz, 1H), 1.09 (s, 3H), 0.94 (d, J=7.0 Hz, 3H), 0.91 (d, J=6.4 Hz, 3H), 0.76 (t, J=12.2 Hz, 1H); MS: MS *m/z* 854.5 (M^++1).

Preparation of Compound 1186

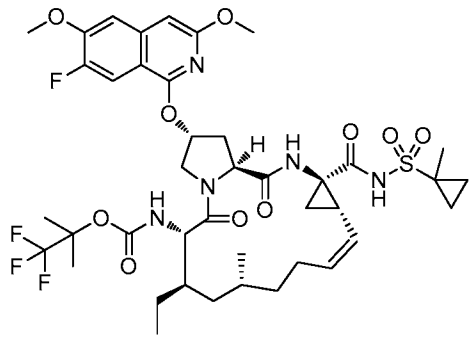


Compound 1186

Compounds 1186 was prepared using 1,7-difluoro-6-methoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1186: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 854.5 (M^++1).

Preparation of Compound 1187

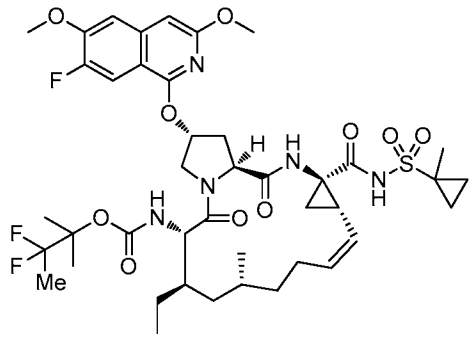


Compound 1187

Compounds 1187 was prepared using 1,7-difluoro-3,6-dimethoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1187: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-3,6-dimethoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.67 - 7.60 (m, 1H), 6.98 (d, J=7.7 Hz, 1H), 6.61 (br. s., 1H), 6.51 (s, 1H), 5.89 (br. s., 1H), 5.64 - 5.57 (m, 1H), 5.29 (d, J=7.9 Hz, 1H), 4.99 (t, J=10.0 Hz, 1H), 4.64 (d, J=10.7 Hz, 1H), 4.48 (br. s., 1H), 4.17 - 4.02 (m, 3H), 4.01 (s, 3H), 3.99 (s, 3H), 2.81 - 2.68 (m, 2H), 2.54 (d, J=8.5 Hz, 1H), 2.36 - 2.25 (m, 1H), 1.99 - 1.90 (m, 3H), 1.85 - 1.78 (m, 1H), 1.55 - 1.50 (m, 4H), 1.46 (s, 3H), 1.45 - 1.40 (m, 1H), 1.40 - 1.27 (m, 4H), 1.23 (dd, J=8.3, 4.5 Hz, 1H), 1.12 (t, J=12.2 Hz, 1H), 0.99 (d, J=6.5 Hz, 3H), 0.93 - 0.82 (m, 6H); MS: MS *m/z* 884.5 (M^++1).

Preparation of Compound 1188



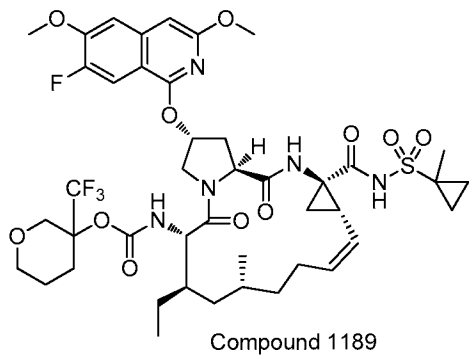
Compound 1188

Compounds 1188 was prepared using 1,7-difluoro-3,6-dimethoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1188: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-3,6-dimethoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.04 (s, 1H), 9.08 (s, 1H), 7.69 (d, J=8.5 Hz, 1H), 7.58 (d, J=11.6 Hz, 1H), 7.39 (d, J=8.5

Hz, 1H), 6.69 (s, 1H), 5.79 (br. s., 1H), 5.57 - 5.50 (m, 1H), 4.99 (t, J=9.8 Hz, 1H), 4.56 - 4.48 (m, 2H), 3.96 (s, 3H), 3.95 - 3.91 (m, 2H), 3.90 (s, 3H), 2.75 - 2.62 (m, 2H), 2.39 - 2.28 (m, 2H), 1.94 (d, J=13.1 Hz, 2H), 1.65 - 1.55 (m, 3H), 1.55 - 1.49 (m, 2H), 1.49 - 1.42 (m, 3H), 1.41 (s, 3H), 1.32 (s, 3H), 1.31 - 1.23 (m, 1H), 1.18 (br. s., 1H), 1.10 (s, 3H), 1.03 (t, J=12.4 Hz, 1H), 0.93 (d, J=6.1 Hz, 3H), 0.90 (br. s., 2H), 0.76 (t, J=7.5 Hz, 3H); MS: MS *m/z* 880.6 (M^++1).

Preparation of Compound 1189



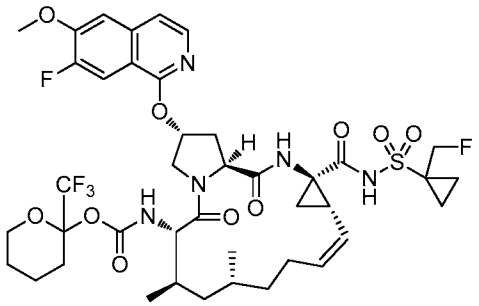
Compound 1189

Compounds 1189 was prepared using 1,7-difluoro-3,6-dimethoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1189: 3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-3,6-dimethoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.02 (s, 1H), 9.08 (s, 1H), 8.00 (d, J=8.2 Hz, 1H), 7.56 (d, J=11.6 Hz, 1H), 7.38 (d, J=8.2 Hz, 1H), 6.69 - 6.66 (m, 1H), 5.78 (br. s., 1H), 5.54 (d, J=6.7 Hz, 1H), 4.99 (t, J=9.8 Hz, 1H), 4.54 - 4.44 (m, 2H), 3.99 (d, J=4.0 Hz, 2H), 3.96 (s, 3H), 3.95 - 3.91 (m, 1H), 3.89 (s, 3H), 3.59 (d, J=11.0 Hz, 1H), 3.51 - 3.37 (m, 3H), 2.75 - 2.68 (m, 1H), 2.68 - 2.61 (m, 1H), 2.36 - 2.23 (m, 3H), 2.01 (br. s., 1H), 1.92 (br. s., 1H), 1.83 - 1.76 (m, 1H), 1.70 - 1.59 (m, 3H), 1.55 - 1.42 (m, 6H), 1.41 (s, 3H), 1.37 (s, 2H), 1.29

(d, J=10.7 Hz, 2H), 1.03 (t, J=12.2 Hz, 1H), 0.93 (d, J=6.4 Hz, 3H), 0.90 (br. s., 2H), 0.76 (t, J=7.5 Hz, 3H); MS: MS *m/z* 926.6 (M^++1).

Preparation of Compound 1190

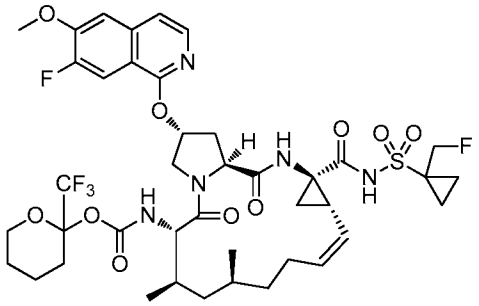


Compound 1190

Compounds 1190 was prepared using 1,7-difluoro-6-methoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1190: 2-(trifluoromethyl)tetrahydro-2H-pyran-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.26 (s, 1H), 9.02 (s, 1H), 7.98 (d, J=5.8 Hz, 1H), 7.93 (d, J=7.9 Hz, 1H), 7.69 (d, J=11.6 Hz, 1H), 7.56 (d, J=8.2 Hz, 1H), 7.36 (d, J=5.8 Hz, 1H), 5.81 (br. s., 1H), 5.55 - 5.49 (m, 1H), 5.01 (t, J=9.8 Hz, 1H), 4.88 - 4.70 (m, J=11.3 Hz, 1H), 4.58 (d, J=11.3 Hz, 1H), 4.54 - 4.44 (m, 3H), 3.99 (s, 3H), 3.99 - 3.90 (m, 3H), 3.75 (dd, J=10.7, 8.2 Hz, 1H), 3.61 - 3.55 (m, 1H), 3.46 - 3.39 (m, 2H), 2.71 - 2.58 (m, 2H), 2.35 - 2.27 (m, 2H), 2.22 (d, J=13.4 Hz, 1H), 1.94 - 1.83 (m, 2H), 1.81 - 1.60 (m, 3H), 1.56 - 1.51 (m, 3H), 1.51 - 1.34 (m, 3H), 1.29 - 1.10 (m, 3H), 0.94 (d, J=6.7 Hz, 3H), 0.92 (d, J=6.4 Hz, 3H), 0.76 (t, J=12.5 Hz, 1H); MS: MS *m/z* 900.5 (M^++1).

Preparation of Compound 1191

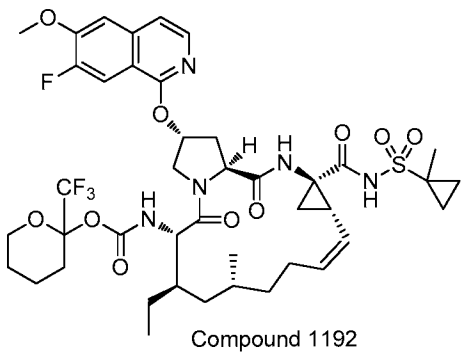


Compound 1191

Compounds 1191 was prepared using 1,7-difluoro-6-methoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1191: 2-(trifluoromethyl)tetrahydro-2H-pyran-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ; MS: MS *m/z* 900.5 (M^++1).

Preparation of Compound 1192

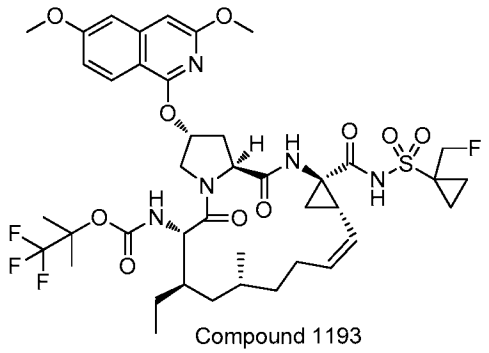


Compound 1192

Compounds 1192 was prepared using 1,7-difluoro-6-methoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1192: 2-(trifluoromethyl)tetrahydro-2H-pyran-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.00 (br. s., 1H), 9.08 (br. s., 1H), 8.00 - 7.94 (m, 2H), 7.68 (d, J=11.3 Hz, 1H), 7.56 (d, J=8.2 Hz, 1H), 7.36 (d, J=5.8 Hz, 1H), 5.83 (br. s., 1H), 5.52 (br. s., 1H), 5.00 (br. s., 1H), 4.55 - 4.46 (m, 2H), 3.99 (s, 3H), 3.98 - 3.92 (m, 2H), 3.59 - 3.54 (m, 1H), 3.44 - 3.37 (m, 2H), 2.70 (br. s., 1H), 2.60 (br. s., 1H), 2.39 - 2.27 (m, 2H), 2.22 (d, J=13.1 Hz, 1H), 2.00 (br. s., 1H), 1.96 - 1.87 (m, 1H), 1.80 - 1.73 (m, 1H), 1.69 - 1.58 (m, 2H), 1.56 (br. s., 1H), 1.55 - 1.42 (m, 5H), 1.41 (s, 4H), 1.35 (br. s., 2H), 1.28 (br. s., 1H), 1.17 (br. s., 1H), 1.02 (t, J=12.5 Hz, 1H), 0.93 (d, J=6.7 Hz, 3H), 0.89 (br. s., 1H), 0.83 (d, J=7.6 Hz, 1H), 0.75 (t, J=7.5 Hz, 3H); MS: MS *m/z* 896.7 (M^++1).

Preparation of Compound 1193

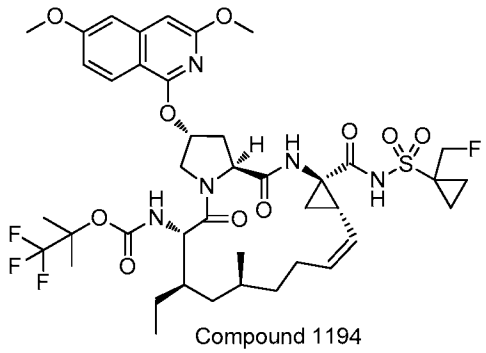


Compound 1193

Compounds 1193 was prepared using 1-fluoro-3,6-dimethoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1193: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.26 (br. s., 1H), 9.04 (br. s., 1H), 7.89 - 7.82 (m, 2H), 7.14 (d, J=2.4 Hz, 1H), 6.89 (dd, J=9.0, 2.3 Hz, 1H), 6.62 (s, 1H), 5.77 (br. s., 1H), 5.50 (br. s., 1H), 4.99 (br. s., 1H), 4.89 - 4.68 (m, 1H), 4.59 (d, J=11.6 Hz, 1H), 4.55 - 4.43 (m, 3H), 3.93 (dd, J=8.2, 4.9 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 2.63 (br. s., 2H), 2.51 (br. s., 3H), 2.35 - 2.24 (m, 2H), 1.98 - 1.85 (m, 2H), 1.51 (br. s., 3H), 1.44 (br. s., 2H), 1.41 (s, 3H), 1.34 (br. s., 2H), 1.22 (d, J=11.0 Hz, 3H), 1.16 (s, 3H), 0.98 (d, J=11.3 Hz, 1H), 0.92 (d, J=6.4 Hz, 2H), 0.73 (t, J=7.3 Hz, 3H); MS: MS *m/z* 884.7 (M^++1).

Preparation of Compound 1194

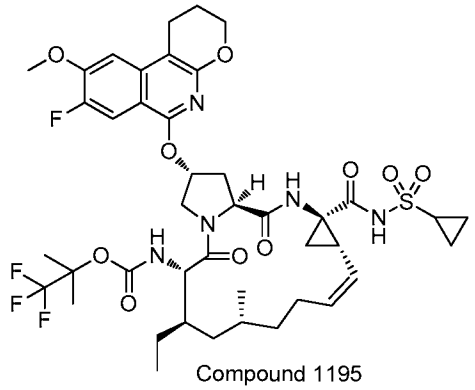


Compound 1194

Compounds 1194 was prepared using 1-fluoro-3,6-dimethoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1194: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 884.7 (M^++1).

Preparation of Compound 1195

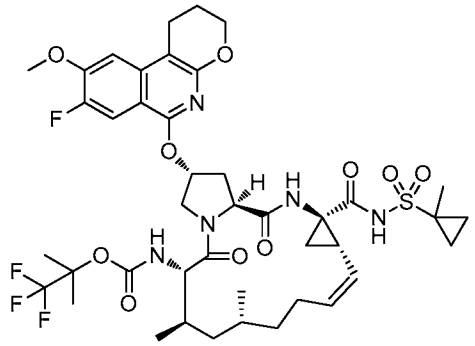


Compound 1195

Compounds 1195 was prepared using 6,8-difluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1195: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((8-fluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.12 (br. s., 1H), 8.92 (br. s., 1H), 7.79 (d, J=8.2 Hz, 1H), 7.59 (d, J=11.3 Hz, 1H), 7.16 (d, J=7.9 Hz, 1H), 5.64 (br. s., 1H), 5.49 (br. s., 1H), 5.09 (br. s., 1H), 4.48 (d, J=11.3 Hz, 1H), 4.44 - 4.39 (m, 1H), 4.25 (t, J=5.2 Hz, 2H), 3.98 (s, 3H), 3.90 - 3.83 (m, 2H), 2.83 (br. s., 3H), 2.59 (br. s., 2H), 2.31 - 2.20 (m, 2H), 2.02 (br. s., 2H), 1.95 - 1.83 (m, 2H), 1.57 (br. s., 1H), 1.49 (br. s., 3H), 1.44 (br. s., 1H), 1.40 (s, 3H), 1.32 (br. s., 2H), 1.15 (s, 3H), 1.06 (br. s., 3H), 1.03 - 0.93 (m, 3H), 0.91 (d, J=6.7 Hz, 3H), 0.72 (t, J=7.3 Hz, 3H); MS: MS *m/z* 896.8 (M^++1).

Preparation of Compound 1196

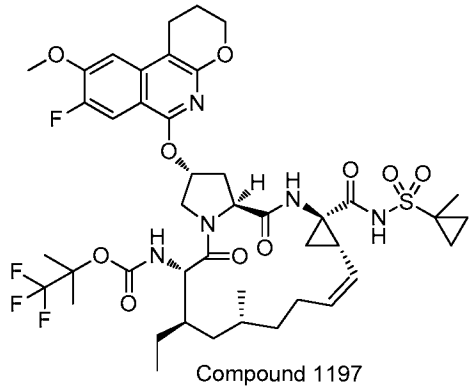


Compound 1196

Compounds 1196 was prepared using 6,8-difluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1196: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((8-fluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.01 (br. s., 1H), 9.07 (br. s., 1H), 7.76 (d, J=7.6 Hz, 1H), 7.62 (d, J=11.3 Hz, 1H), 7.16 (d, J=7.9 Hz, 1H), 5.64 (br. s., 1H), 5.49 (br. s., 1H), 5.00 (br. s., 1H), 4.51 - 4.43 (m, 2H), 4.27 - 4.21 (m, 2H), 3.97 (s, 3H), 3.85 (d, J=8.9 Hz, 1H), 2.83 (br. s., 2H), 2.59 (br. s., 2H), 2.33 - 2.20 (m, 2H), 2.02 (d, J=4.9 Hz, 2H), 1.85 (br. s., 1H), 1.80 (d, J=7.6 Hz, 1H), 1.70 - 1.64 (m, 1H), 1.58 (br. s., 1H), 1.48 (br. s., 1H), 1.43 - 1.40 (m, 1H), 1.38 (d, J=5.8 Hz, 7H), 1.35 - 1.29 (m, 2H), 1.25 (br. s., 1H), 1.20 - 1.13 (m, 1H), 1.12 (s, 3H), 0.90 (d, J=6.7 Hz, 3H), 0.87 (d, J=6.1 Hz, 3H), 0.85 - 0.80 (m, 2H), 0.72 (t, J=12.1 Hz, 1H); MS: MS *m/z* 896.7 (M^++1).

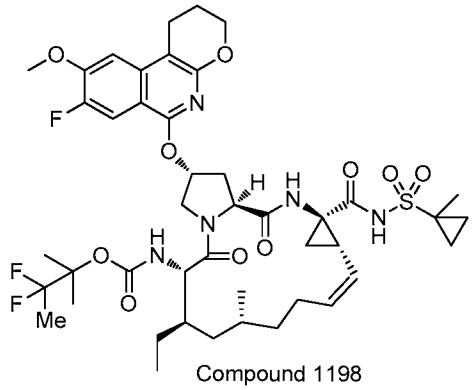
Preparation of Compound 1197



Compounds 1197 was prepared using 6,8-difluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1197: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((8-fluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (400MHz, CD_3OD) δ 7.65 (d, J=11.5 Hz, 1H), 7.11 (d, J=8.0 Hz, 1H), 5.76 (br. s., 1H), 5.57 (td, J=10.1, 5.9 Hz, 1H), 5.06 (br. s., 1H), 4.72 (d, J=11.0 Hz, 1H), 4.61 (dd, J=10.3, 7.0 Hz, 1H), 4.39 - 4.32 (m, 2H), 4.05 (s, 1H), 4.01 (s, 3H), 3.97 (dd, J=11.8, 3.3 Hz, 1H), 2.92 - 2.86 (m, 2H), 2.74 - 2.63 (m, 2H), 2.40 (ddd, J=13.7, 10.2, 4.1 Hz, 2H), 2.20 - 2.11 (m, 2H), 2.00 - 1.90 (m, 2H), 1.74 (dd, J=8.5, 5.5 Hz, 1H), 1.67 - 1.51 (m, 5H), 1.50 (s, 3H), 1.49 - 1.41 (m, 2H), 1.40 (s, 4H), 1.31 - 1.22 (m, 1H), 1.18 - 1.10 (m, 1H), 1.08 (s, 3H), 0.99 (d, J=6.8 Hz, 3H), 0.87 - 0.80 (m, 5H); MS: MS *m/z* 910.9 (M^++1).

Preparation of Compound 1198

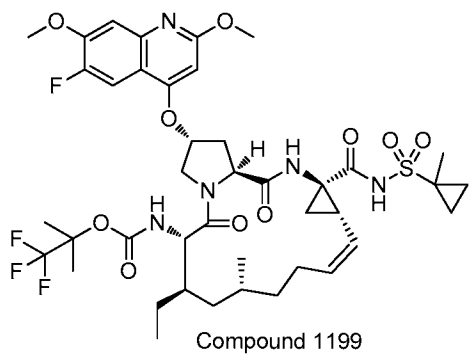


Compound 1198

Compounds 1198 was prepared using 6,8-difluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1198: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((8-fluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (400MHz, CD_3OD) δ 7.64 (d, J=11.5 Hz, 1H), 7.11 (d, J=8.0 Hz, 1H), 5.77 (br. s., 1H), 5.58 (td, J=10.2, 6.0 Hz, 1H), 5.01 (t, J=9.5 Hz, 1H), 4.72 (d, J=11.5 Hz, 1H), 4.65 - 4.58 (m, 1H), 4.40 - 4.32 (m, 2H), 4.08 - 4.02 (m, 1H), 4.01 (s, 3H), 3.98 (dd, J=11.9, 3.4 Hz, 1H), 2.92 - 2.86 (m, 2H), 2.75 - 2.65 (m, 2H), 2.47 - 2.35 (m, 2H), 2.20 - 2.11 (m, 2H), 2.00 - 1.88 (m, 2H), 1.75 (dd, J=8.3, 5.5 Hz, 1H), 1.65 - 1.58 (m, 2H), 1.57 (s, 1H), 1.56 - 1.53 (m, 2H), 1.52 (s, 2H), 1.51 (s, 3H), 1.48 (s, 1H), 1.44 - 1.36 (m, 2H), 1.31 (s, 3H), 1.30 - 1.21 (m, 1H), 1.16 - 1.06 (m, 1H), 1.00 - 0.97 (m, 5H), 0.89 - 0.85 (m, 2H), 0.83 (t, J=7.4 Hz, 3H); MS: MS *m/z* 906.9 (M^++1).

Preparation of Compound 1199

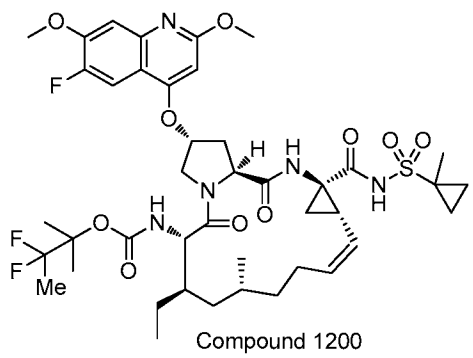


Compound 1199

Compounds 1199 was prepared using 4,6-difluoro-2,7-dimethoxyquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1199: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-2,7-dimethoxyquinolin-4-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 10.95 (br. s., 1H), 9.08 (br. s., 1H), 7.88 (d, J=7.6 Hz, 1H), 7.53 (d, J=11.6 Hz, 1H), 7.31 (d, J=8.2 Hz, 1H), 6.50 (s, 1H), 5.50 (br. s., 1H), 5.44 (br. s., 1H), 5.00 (br. s., 1H), 4.53 (d, J=11.6 Hz, 1H), 4.46 - 4.41 (m, 1H), 3.95 (s, 7H), 3.90 (t, J=10.1 Hz, 2H), 2.60 (br. s., 2H), 2.33 - 2.21 (m, 2H), 1.98 - 1.85 (m, 2H), 1.57 (br. s., 2H), 1.47 (br. s., 4H), 1.41 (s, 3H), 1.39 (s, 3H), 1.32 (br. s., 1H), 1.25 (br. s., 2H), 1.18 (s, 3H), 0.99 (t, J=12.4 Hz, 1H), 0.91 (d, J=6.4 Hz, 3H), 0.85 (br. s., 2H), 0.74 (t, J=7.3 Hz, 3H); MS: MS *m/z* 884.7 (M^++1).

Preparation of Compound 1200

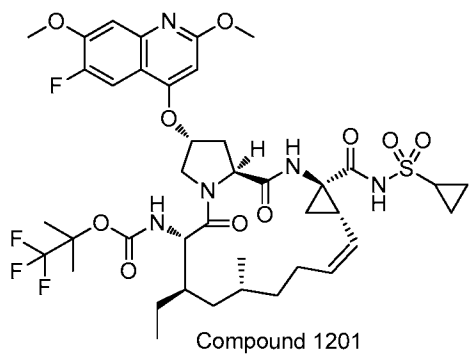


Compound 1200

Compounds 1200 was prepared using 4,6-difluoro-2,7-dimethoxyquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1200: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-2,7-dimethoxyquinolin-4-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 10.97 (br. s., 1H), 9.06 (br. s., 1H), 7.66 (d, J=8.2 Hz, 1H), 7.53 (d, J=11.6 Hz, 1H), 7.31 (d, J=7.9 Hz, 1H), 6.50 (s, 1H), 5.51 (br. s., 1H), 5.44 (br. s., 1H), 5.01 (br. s., 1H), 4.55 (d, J=11.9 Hz, 1H), 4.46 - 4.41 (m, 1H), 3.95 (s, 6H), 3.93 - 3.84 (m, 2H), 2.62 (d, J=14.6 Hz, 2H), 2.35 - 2.21 (m, 2H), 1.92 (d, J=7.6 Hz, 2H), 1.63 - 1.47 (m, 6H), 1.44 (br. s., 3H), 1.40 (s, 3H), 1.33 (br. s., 1H), 1.31 (s, 3H), 1.23 (br. s., 2H), 1.16 (br. s., 1H), 1.07 (s, 3H), 1.00 (t, J=12.1 Hz, 1H), 0.92 (d, J=5.5 Hz, 3H), 0.87 (br. s., 2H), 0.74 (t, J=7.2 Hz, 3H); MS: MS *m/z* 881.0 (M^++1).

Preparation of Compound 1201

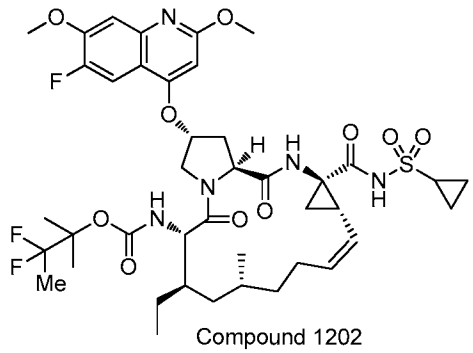


Compound 1201

Compounds 1201 was prepared using 4,6-difluoro-2,7-dimethoxyquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1201: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((6-fluoro-2,7-dimethoxyquinolin-4-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.13 (br. s., 1H), 8.93 (br. s., 1H), 7.87 (d, J=8.2 Hz, 1H), 7.53 (d, J=11.6 Hz, 1H), 7.31 (d, J=8.2 Hz, 1H), 6.50 (s, 1H), 5.50 (br. s., 1H), 5.43 (br. s., 1H), 5.09 (br. s., 1H), 4.53 (d, J=11.6 Hz, 1H), 4.42 - 4.37 (m, 1H), 3.97 - 3.94 (m, 6H), 3.92 - 3.83 (m, 2H), 2.89 (br. s., 1H), 2.60 (br. s., 2H), 2.30 - 2.21 (m, 2H), 1.97 - 1.86 (m, 2H), 1.57 (br. s., 1H), 1.53 (br. s., 2H), 1.45 (br. s., 2H), 1.42 (s, 3H), 1.33 (br. s., 2H), 1.20 (s, 3H), 1.07 (br. s., 3H), 0.97 (d, J=11.0 Hz, 3H), 0.92 (d, J=6.7 Hz, 3H), 0.73 (t, J=7.5 Hz, 3H); MS: MS *m/z* 870.7 (M^++1).

Preparation of Compound 1202

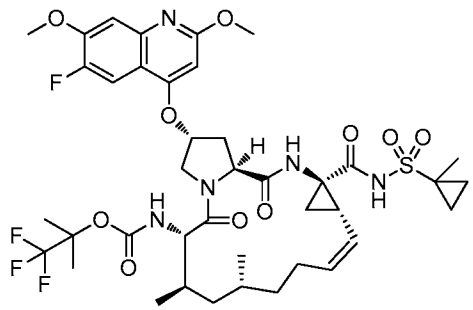


Compound 1202

Compounds 1202 was prepared using 4,6-difluoro-2,7-dimethoxyquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1202: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((6-fluoro-2,7-dimethoxyquinolin-4-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.13 (br. s., 1H), 8.93 (br. s., 1H), 7.65 (d, J=8.5 Hz, 1H), 7.53 (d, J=11.9 Hz, 1H), 7.31 (d, J=7.9 Hz, 1H), 6.50 (s, 1H), 5.50 (br. s., 1H), 5.43 (br. s., 1H), 5.09 (br. s., 1H), 4.54 (d, J=12.2 Hz, 1H), 4.40 (dd, J=10.1, 7.0 Hz, 1H), 3.95 (s, 6H), 3.94 - 3.84 (m, 3H), 2.89 (br. s., 1H), 2.62 (d, J=12.8 Hz, 2H), 2.31 - 2.21 (m, 2H), 1.91 (br. s., 2H), 1.63 - 1.49 (m, 6H), 1.44 (br. s., 2H), 1.35 (d, J=15.9 Hz, 2H), 1.31 (s, 3H), 1.16 (br. s., 2H), 1.08 (s, 3H), 0.97 (d, J=10.4 Hz, 3H), 0.92 (d, J=6.1 Hz, 3H), 0.74 (t, J=7.3 Hz, 3H); MS: MS *m/z* 867.0 (M^++1).

Preparation of Compound 1203

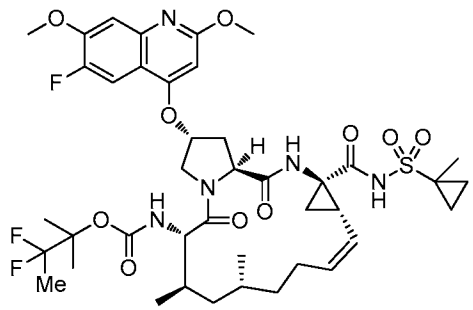


Compound 1203

Compounds 1203 was prepared using 4,6-difluoro-2,7-dimethoxyquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1203: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-fluoro-2,7-dimethoxyquinolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.01 (br. s., 1H), 9.12 (br. s., 1H), 7.73 (d, J=8.9 Hz, 1H), 7.63 (d, J=11.9 Hz, 1H), 7.31 - 7.24 (m, 1H), 6.25 (s, 1H), 5.78 (br. s., 1H), 5.50 (br. s., 1H), 4.99 (br. s., 1H), 4.43 (t, J=8.5 Hz, 1H), 4.33 (d, J=11.0 Hz, 1H), 3.93 (s, 3H), 3.95 (s, 3H), 2.60 (br. s., 1H), 2.55 (s, 2H), 2.27 (br. s., 2H), 1.93 - 1.86 (m, 1H), 1.83 (d, J=5.8 Hz, 1H), 1.65 - 1.55 (m, 2H), 1.47 (d, J=10.1 Hz, 1H), 1.38 (s, 5H), 1.32 (s, 4H), 1.25 (d, J=9.5 Hz, 1H), 1.20 (s, 3H), 1.11 (br. s., 1H), 0.90 (d, J=6.4 Hz, 4H), 0.83 (d, J=6.1 Hz, 5H), 0.70 (t, J=12.4 Hz, 1H); MS: MS *m/z* 870.8 (M^++1).

Preparation of Compound 1204

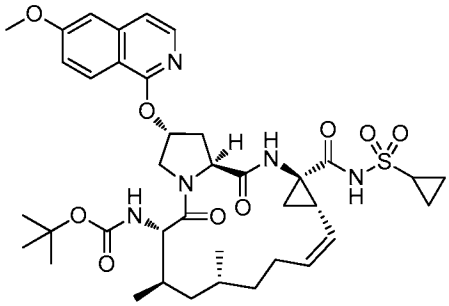


Compound 1204

Compounds 1204 was prepared using 4,6-difluoro-2,7-dimethoxyquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1204: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-fluoro-2,7-dimethoxyquinolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.15 (s, 1H), 9.08 (br. s., 1H), 7.63 (d, J=11.9 Hz, 1H), 7.52 (d, J=8.5 Hz, 1H), 7.29 (d, J=8.2 Hz, 1H), 6.25 (s, 1H), 5.78 (br. s., 1H), 5.49 (br. s., 1H), 5.03 (br. s., 1H), 4.42 (t, J=8.1 Hz, 1H), 4.30 (d, J=9.8 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.27 (br. s., 2H), 1.95 - 1.84 (m, 1H), 1.80 (br. s., 1H), 1.56 (t, J=19.7 Hz, 5H), 1.46 (br. s., 1H), 1.38 (s, 4H), 1.35 - 1.25 (m, 2H), 1.22 (s, 3H), 1.18 - 1.13 (m, 1H), 1.10 (s, 3H), 0.90 (d, J=6.7 Hz, 3H), 0.83 (d, J=5.8 Hz, 3H), 0.70 (t, J=11.7 Hz, 1H); MS: MS *m/z* 866.8 (M^{+}+1).

Preparation of Compound 1205

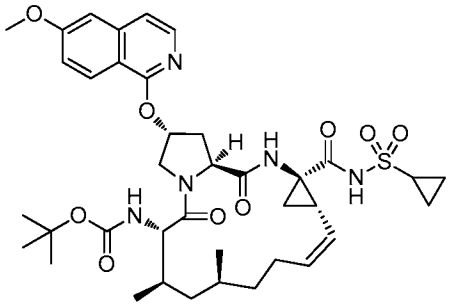


Compound 1205

Compounds 1205 was prepared using 1-chloro-6-methoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1205: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, $CDCl_3$) 0.72 - 0.83 (m, 2 H) 0.88 - 0.94 (m, 1 H) 0.99 (d, J=7.02 Hz, 6 H) 1.05 - 1.13 (m, 2 H) 1.15 (d, J=10.07 Hz, 2 H) 1.20 (s, 9 H) 1.35 - 1.40 (m, 2 H) 1.40 - 1.48 (m, 2 H) 1.48 - 1.51 (m, 1 H) 1.64 - 1.72 (m, 1 H) 1.72 - 1.86 (m, 1 H) 1.92 - 1.99 (m, 2 H) 2.21 - 2.36 (m, 1 H) 2.44 - 2.56 (m, 1 H) 2.66 - 2.78 (m, 1 H) 2.86 - 2.97 (m, 1 H) 3.92 (s, 3 H) 3.99 - 4.09 (m, 1 H) 4.38 - 4.46 (m, 1 H) 4.71 (d, J=10.68 Hz, 1 H) 4.93 (t, J=9.92 Hz, 1 H) 5.51 - 5.65 (m, 1 H) 5.87 - 6.00 (m, 1 H) 7.01 (s, 1 H) 7.05 (d, J=8.55 Hz, 1 H) 7.16 (d, J=5.19 Hz, 1 H) 7.93 (d, J=5.80 Hz, 1 H) 8.03 (d, J=8.85 Hz, 1 H) 10.42 (s, 1 H); MS: MS *m/z* 754.4 (M^++1).

Preparation of Compound 1206

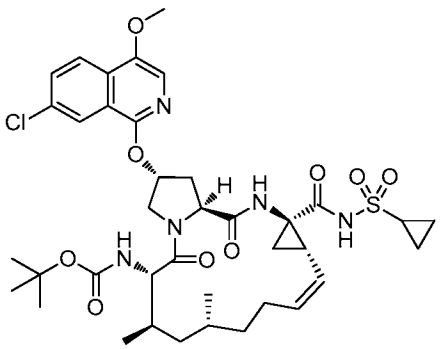


Compound 1206

Compounds 1206 was prepared using 1-chloro-6-methoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1206: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 754.4 (M^++1).

Preparation of Compound 1207

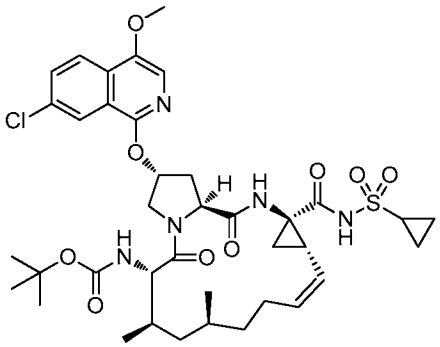


Compound 1207

Compounds 1207 was prepared using 1,7-dichloro-4-methoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1207: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-chloro-4-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, $CDCl_3$) δ 0.74 - 0.84 (m, 2 H) 0.86 (d, J=6.41 Hz, 1 H) 0.88 - 0.94 (m, 1 H) 0.97 (t, J=5.95 Hz, 6 H) 1.06 - 1.16 (m, 9 H) 1.40 - 1.54 (m, 4 H) 1.64 - 1.71 (m, 1 H) 1.74 - 1.87 (m, 1 H) 1.88 - 1.99 (m, 2 H) 2.22 - 2.35 (m, 1 H) 2.43 - 2.54 (m, 1 H) 2.63 - 2.71 (m, 1 H) 2.75 (q, J=8.65 Hz, 1 H) 2.83 - 2.96 (m, 1 H) 3.89 (t, J=9.92 Hz, 1 H) 3.97 - 4.00 (m, 3 H) 4.01 (d, J=3.66 Hz, 1 H) 4.43 - 4.59 (m, 1 H) 4.67 (d, J=10.99 Hz, 1 H) 4.92 (t, J=9.31 Hz, 1 H) 5.49 - 5.59 (m, 1 H) 5.72 - 5.89 (m, 2 H) 7.40 - 7.52 (m, 1 H) 7.56 - 7.65 (m, 1 H) 7.98 (d, J=1.83 Hz, 1 H) 8.00 - 8.11 (m, 1 H) 10.42 - 10.57 (m, 1 H); MS: MS *m/z* 788.4 (M^++1).

Preparation of Compound 1208

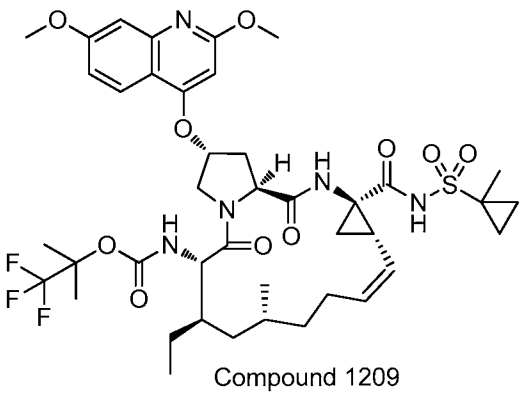


Compound 1208

Compounds 1208 was prepared using 1,7-dichloro-4-methoxyisoquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1208: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-chloro-4-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 788.3 (M^++1).

Preparation of Compound 1209

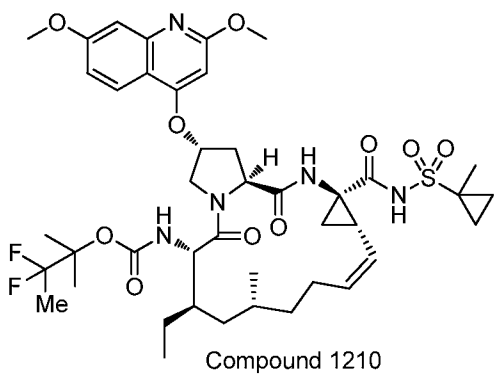


Compound 1209

Compounds 1209 was prepared using 4-fluoro-2,7-dimethoxyquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1209: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,7-dimethoxyquinolin-4-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 10.98 (br. s., 1H), 9.10 (br. s., 1H), 7.88 (d, J=7.9 Hz, 1H), 7.80 (d, J=9.5 Hz, 1H), 7.12 (br. s., 1H), 6.91 (d, J=7.3 Hz, 1H), 6.42 (s, 1H), 5.51 (br. s., 1H), 5.43 (br. s., 1H), 4.98 (br. s., 1H), 4.55 (d, J=12.2 Hz, 1H), 4.43 (d, J=7.6 Hz, 1H), 3.95 (s, 3H), 3.90 (d, J=11.0 Hz, 2H), 3.86 (s, 3H), 2.64 (br. s., 2H), 2.33 - 2.21 (m, 2H), 1.99 - 1.87 (m, 2H), 1.59 (br. s., 1H), 1.50 (br. s., 2H), 1.41 (d, J=7.0 Hz, 6H), 1.33 (br. s., 2H), 1.25 (d, J=16.8 Hz, 3H), 1.15 (br. s., 5H), 1.00 (br. s., 1H), 0.94 - 0.84 (m, 5H), 0.73 (t, J=7.2 Hz, 3H); MS: MS *m/z* 866.5 (M^++1).

Preparation of Compound 1210

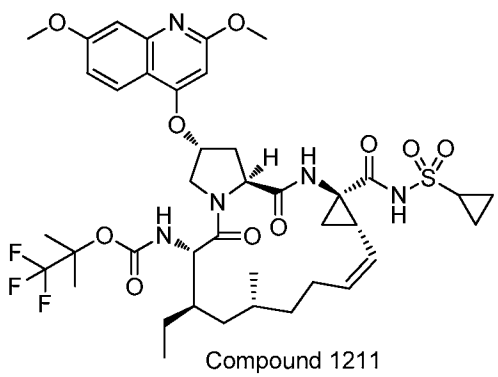


Compound 1210

Compounds 1210 was prepared using 4-fluoro-2,7-dimethoxyquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1210: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,7-dimethoxyquinolin-4-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.12 (br. s., 1H), 8.95 (br. s., 1H), 7.85 (d, J=8.2 Hz, 1H), 7.80 (d, J=8.5 Hz, 1H), 7.12 (br. s., 1H), 6.90 (d, J=8.9 Hz, 1H), 6.41 (s, 1H), 5.54 - 5.47 (m, 1H), 5.42 (br. s., 1H), 5.07 (br. s., 1H), 4.54 (d, J=11.6 Hz, 1H), 4.42 - 4.37 (m, 1H), 3.95 (s, 3H), 3.89 (d, J=9.5 Hz, 2H), 3.86 (s, 3H), 2.89 (br. s., 1H), 2.61 (br. s., 2H), 2.24 (br. s., 2H), 1.91 (br. s., 2H), 1.57 (br. s., 1H), 1.52 (br. s., 2H), 1.47 - 1.44 (m, 2H), 1.41 (br. s., 4H), 1.34 (br. s., 2H), 1.22 (d, J=11.6 Hz, 1H), 1.15 (br. s., 4H), 1.08 (br. s., 3H), 0.98 (br. s., 4H), 0.92 (d, J=4.6 Hz, 4H), 0.73 (t, J=7.3 Hz, 3H); MS: MS *m/z* 862.6 (M^{+}+1).

Preparation of Compound 1211

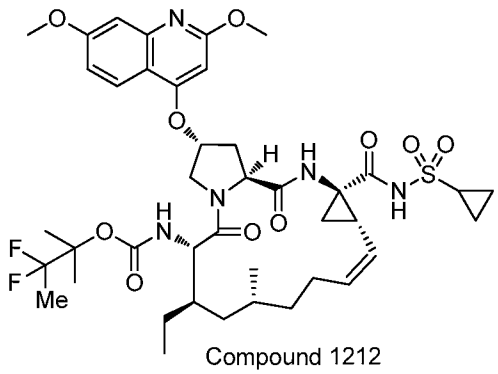


Compound 1211

Compounds 1211 was prepared using 4-fluoro-2,7-dimethoxyquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1211: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,7-dimethoxyquinolin-4-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.13 (br. s., 1H), 8.97 (br. s., 1H), 7.87 (d, J=7.6 Hz, 1H), 7.80 (d, J=8.5 Hz, 1H), 7.12 (br. s., 1H), 6.90 (d, J=9.2 Hz, 1H), 6.41 (br. s., 1H), 5.51 (d, J=6.1 Hz, 1H), 5.42 (br. s., 1H), 5.06 (t, J=9.0 Hz, 1H), 4.55 (d, J=12.2 Hz, 1H), 4.40 (br. s., 1H), 3.95 (br. s., 3H), 3.90 (br. s., 2H), 3.86 (br. s., 3H), 2.90 (br. s., 1H), 2.64 (d, J=7.3 Hz, 2H), 2.25 (d, J=8.9 Hz, 2H), 1.92 (br. s., 2H), 1.58 (br. s., 1H), 1.53 (br. s., 2H), 1.42 (br. s., 5H), 1.34 (br. s., 2H), 1.23 (br. s., 1H), 1.17 (br. s., 3H), 1.09 (br. s., 3H), 0.99 (br. s., 2H), 0.92 (br. s., 3H), 0.73 (br. s., 3H); MS: MS *m/z* 852.5 (M^{+}+1).

Preparation of Compound 1212

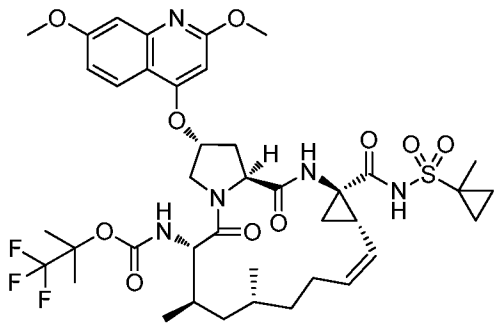


Compound 1212

Compounds 1212 was prepared using 4-fluoro-2,7-dimethoxyquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1212: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,7-dimethoxyquinolin-4-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 11.13 (br. s., 1H), 8.91 (br. s., 1H), 7.80 (d, J=8.5 Hz, 1H), 7.65 (d, J=8.2 Hz, 1H), 7.12 (br. s., 1H), 6.89 (d, J=8.5 Hz, 1H), 6.41 (s, 1H), 5.49 (br. s., 1H), 5.42 (br. s., 1H), 5.10 (br. s., 1H), 4.54 (d, J=11.9 Hz, 1H), 4.37 (t, J=8.2 Hz, 1H), 3.98 - 3.82 (m, 8H), 2.87 (br. s., 1H), 2.61 (br. s., 2H), 2.25 (br. s., 2H), 1.92 (br. s., 2H), 1.62 - 1.49 (m, 6H), 1.44 (br. s., 3H), 1.33 (br. s., 4H), 1.23 (br. s., 1H), 1.17 (br. s., 1H), 1.09 (br. s., 4H), 1.03 - 0.86 (m, 6H), 0.74 (t, J=6.7 Hz, 3H); MS: MS *m/z* 848.6 (M^++1).

Preparation of Compound 1213

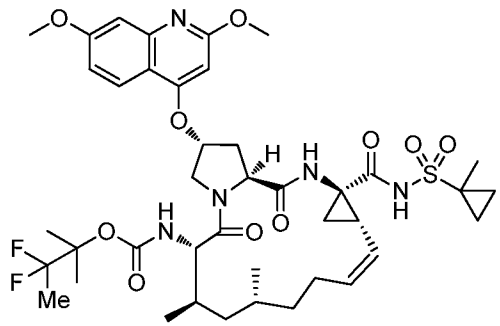


Compound 1213

Compounds 1213 was prepared using 4-fluoro-2,7-dimethoxyquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1213: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,7-dimethoxyquinolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 10.98 (br. s., 1H), 9.10 (br. s., 1H), 7.83 (d, J=8.2 Hz, 2H), 7.12 (br. s., 1H), 6.90 (d, J=8.9 Hz, 1H), 6.40 (s, 1H), 5.51 (br. s., 1H), 5.43 (br. s., 1H), 4.97 (br. s., 1H), 4.55 (d, J=11.6 Hz, 1H), 4.43 (t, J=8.9 Hz, 1H), 3.95 (s, 3H), 3.89 (br. s., 2H), 3.86 (br. s., 3H), 3.72 (t, J=8.7 Hz, 1H), 2.64 (br. s., 2H), 2.34 - 2.20 (m, 2H), 1.85 (br. s., 2H), 1.66 (br. s., 1H), 1.59 (br. s., 1H), 1.51 (br. s., 1H), 1.46 - 1.43 (m, 1H), 1.40 (br. s., 6H), 1.35 (br. s., 2H), 1.32 - 1.21 (m, 2H), 1.18 (br. s., 3H), 1.13 (br. s., 1H), 0.92 (d, J=6.4 Hz, 3H), 0.90 - 0.88 (m, 4H), 0.74 (t, J=12.7 Hz, 1H); MS: MS *m/z* 852.5 (M^++1).

Preparation of Compound 1214

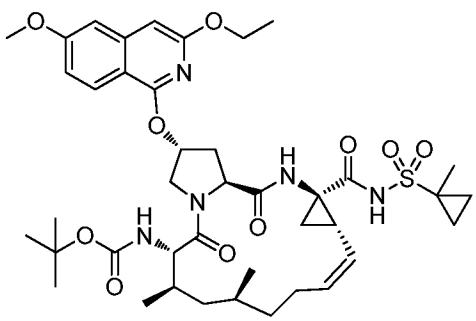


Compound 1214

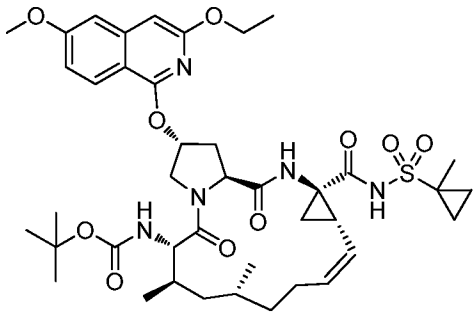
Compounds 1214 was prepared using 4-fluoro-2,7-dimethoxyquinoline and the intermediates described above and by following the general procedure described for the synthesis of Compound 3117.

Compound 1214: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,7-dimethoxyquinolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H-NMR (500MHz, DMSO-d6) δ 10.99 (br. s., 1H), 9.08 (br. s., 1H), 7.83 (d, J=8.9 Hz, 1H), 7.63 (d, J=7.9 Hz, 1H), 7.12 (br. s., 1H), 6.89 (d, J=8.9 Hz, 1H), 6.40 (s, 1H), 5.52 (br. s., 1H), 5.43 (br. s., 1H), 4.98 (br. s., 1H), 4.55 (d, J=11.3 Hz, 1H), 4.41 (d, J=7.0 Hz, 1H), 3.95 (s, 3H), 3.90 (br. s., 1H), 3.86 (s, 3H), 3.75 - 3.68 (m, 1H), 2.70 - 2.58 (m, 2H), 2.35 - 2.20 (m, 2H), 1.89 (br. s., 1H), 1.81 (br. s., 1H), 1.64 (br. s., 1H), 1.58 (t, J=19.4 Hz, 4H), 1.50 (br. s., 1H), 1.42 (br. s., 2H), 1.40 (br. s., 4H), 1.32 (br. s., 4H), 1.23 (br. s., 1H), 1.11 (br. s., 3H), 0.94 - 0.85 (m, 8H), 0.75 (t, J=11.9 Hz, 1H); MS: MS *m/z* 848.6 (M^++1).

Preparation of Compound 3193 and Compound 3194



Compound 3193



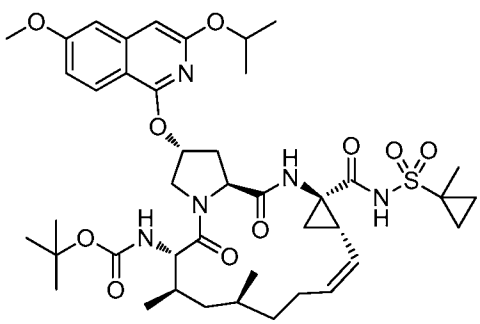
Compound 3194

Compounds 3193 and 3194 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

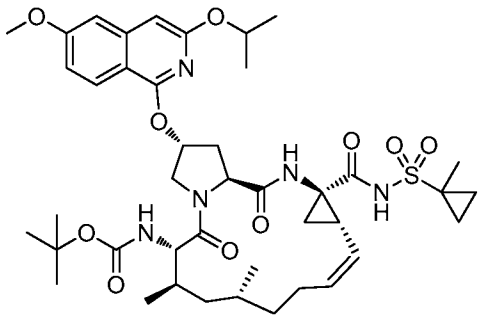
Compound 3193: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 812.6 (M^++1).

Compound 3194: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.09 - 11.00 (m, 1H), 9.14 - 9.02 (m, 1H), 7.91 (d, *J*=9.2 Hz, 1H), 7.21 (d, *J*=7.9 Hz, 1H), 7.12 (d, *J*=1.8 Hz, 1H), 6.85 (dd, *J*=8.9, 2.1 Hz, 1H), 6.58 (s, 1H), 5.80 - 5.74 (m, 1H), 5.60 - 5.47 (m, 1H), 5.03 - 4.90 (m, 1H), 4.57 (d, *J*=9.8 Hz, 1H), 4.45 (t, *J*=7.3 Hz, 1H), 4.28 (q, *J*=6.7 Hz, 2H), 3.96 - 3.90 (m, 1H), 3.87 (s, 3H), 3.74 (dd, *J*=10.4, 8.5 Hz, 1H), 2.78 - 2.57 (m, 2H), 2.40 - 2.24 (m, 2H), 1.97 - 1.77 (m, 2H), 1.75 - 1.66 (m, 1H), 1.63 - 1.56 (m, 1H), 1.54 - 1.04 (m, 21H), 0.97 - 0.82 (m, 8H), 0.74 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 812.6 (M^++1).

Preparation of Compound 3195 and Compound 3196



Compound 3195



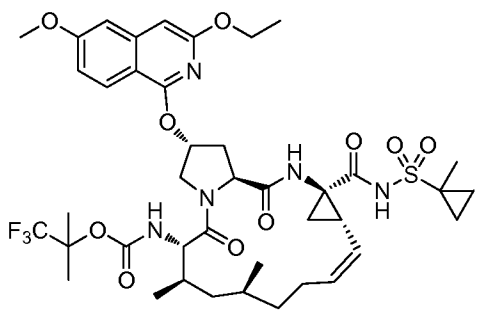
Compound 3196

Compounds 3195 and 3196 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

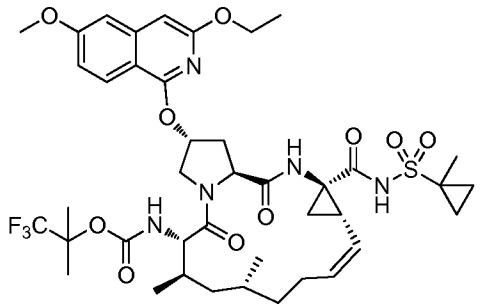
Compound 3195: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 826.6 (M^++1).

Compound 3196: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (br. s., 1H), 9.08 (br. s., 1H), 7.90 (d, *J*=9.2 Hz, 1H), 7.21 (d, *J*=8.2 Hz, 1H), 7.09 (d, *J*=2.1 Hz, 1H), 6.84 (dd, *J*=9.0, 2.3 Hz, 1H), 6.56 (s, 1H), 5.76 (br. s., 1H), 5.61 - 5.48 (m, 1H), 5.18 - 5.06 (m, 1H), 5.02 - 4.90 (m, 1H), 4.58 (d, *J*=11.3 Hz, 1H), 4.46 (t, *J*=8.7 Hz, 1H), 3.97 - 3.91 (m, 1H), 3.86 (s, 3H), 3.78 - 3.71 (m, 1H), 2.77 - 2.57 (m, 2H), 2.40 - 2.25 (m, 2H), 1.97 - 1.78 (m, 2H), 1.74 - 1.66 (m, 1H), 1.64 - 1.58 (m, 1H), 1.55 - 1.05 (m, 24H), 0.98 - 0.85 (m, 8H), 0.74 (t, *J*=12.8 Hz, 1H); MS: MS *m/z* 826.6 (M^++1).

Preparation of Compound 3197 and Compound 3198



Compound 3197



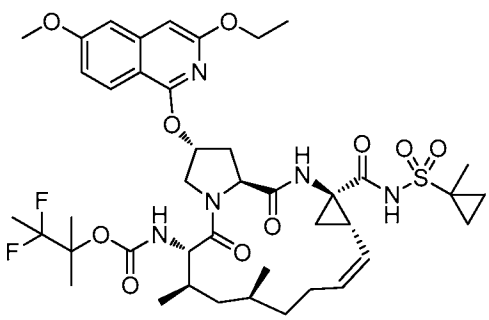
Compound 3198

Compounds 3197 and 3198 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

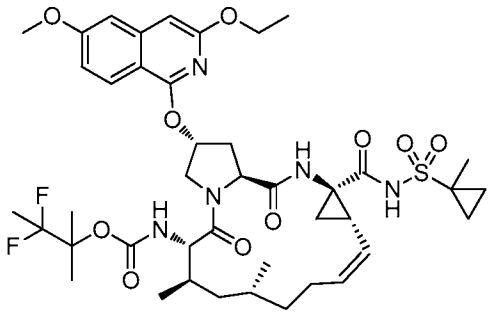
Compound 3197: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 866.5 (M^++1).

Compound 3198: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.12 (br. s., 1H), 7.94 - 7.81 (m, 2H), 7.13 (d, *J*=2.4 Hz, 1H), 6.89 (dd, *J*=9.2, 2.4 Hz, 1H), 6.59 (s, 1H), 5.77 (br. s., 1H), 5.61 - 5.48 (m, 1H), 4.98 (t, *J*=8.9 Hz, 1H), 4.58 - 4.45 (m, 2H), 4.34 - 4.23 (m, 2H), 3.97 - 3.89 (m, 1H), 3.87 (s, 3H), 3.72 (dd, *J*=10.8, 8.1 Hz, 1H), 2.77 - 2.59 (m, 2H), 2.41 - 2.26 (m, 2H), 1.96 - 1.81 (m, 2H), 1.75 - 1.66 (m, 1H), 1.62 (br. s., 1H), 1.57 - 1.09 (m, 18H), 0.92 (dd, *J*=17.9, 6.6 Hz, 8H), 0.76 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 866.6 (M^++1).

Preparation of Compound 3199 and Compound 3200



Compound 3199



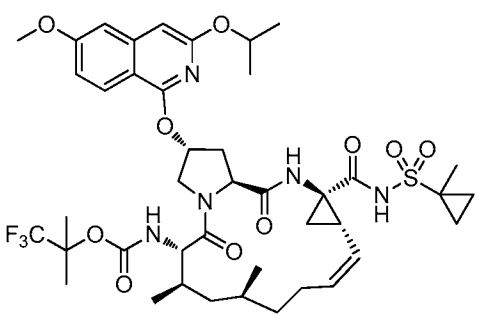
Compound 3200

Compounds 3199 and 3200 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

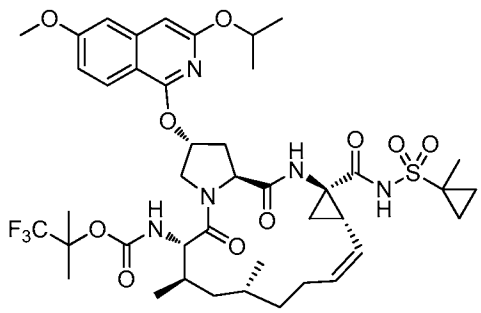
Compound 3199: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 862.6 (M^++1).

Compound 3200: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.12 (br. s., 1H), 7.94 - 7.81 (m, 2H), 7.13 (d, *J*=2.4 Hz, 1H), 6.89 (dd, *J*=9.2, 2.4 Hz, 1H), 6.59 (s, 1H), 5.77 (br. s., 1H), 5.61 - 5.48 (m, 1H), 4.98 (t, *J*=8.9 Hz, 1H), 4.58 - 4.45 (m, 2H), 4.34 - 4.23 (m, 2H), 3.97 - 3.89 (m, 1H), 3.87 (s, 3H), 3.72 (dd, *J*=10.8, 8.1 Hz, 1H), 2.77 - 2.59 (m, 2H), 2.41 - 2.26 (m, 2H), 1.96 - 1.81 (m, 2H), 1.75 - 1.66 (m, 1H), 1.62 (br. s., 1H), 1.57 - 1.09 (m, 18H), 0.92 (dd, *J*=17.9, 6.6 Hz, 8H), 0.76 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 862.6 (M^++1).

Preparation of Compound 3201 and Compound 3202



Compound 3201



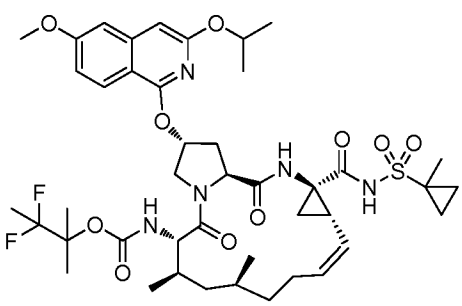
Compound 3202

Compounds 3201 and 3202 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

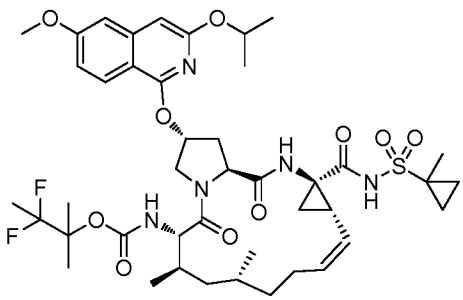
Compound 3201: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 880.7 (M^++1).

Compound 3202: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.12 (s, 1H), 7.91 - 7.83 (m, 2H), 7.11 (d, *J*=2.4 Hz, 1H), 6.88 (dd, *J*=9.2, 2.4 Hz, 1H), 6.57 (s, 1H), 5.77 (br. s., 1H), 5.59 - 5.49 (m, 1H), 5.12 (dquin, *J*=12.2, 6.0 Hz, 1H), 4.98 (t, *J*=9.9 Hz, 1H), 4.59 - 4.44 (m, 2H), 3.94 (dd, *J*=12.1, 4.1 Hz, 1H), 3.86 (s, 3H), 3.72 (dd, *J*=10.7, 7.9 Hz, 1H), 2.73 - 2.57 (m, 2H), 2.41 - 2.24 (m, 2H), 1.97 - 1.79 (m, 2H), 1.74 - 1.65 (m, 1H), 1.65 - 1.59 (m, 1H), 1.57 - 1.08 (m, 21H), 0.92 (dd, *J*=19.1, 6.6 Hz, 8H), 0.76 (t, *J*=12.7 Hz, 1H); MS: MS *m/z* 880.7 (M^++1).

Preparation of Compound 3203 and Compound 3204



Compound 3203



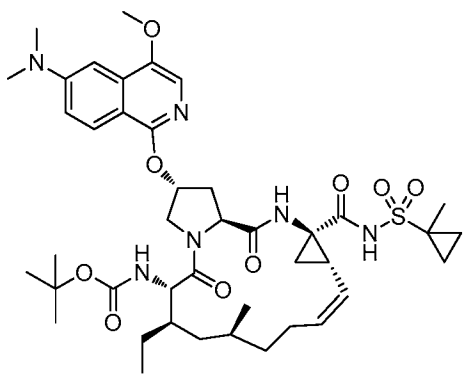
Compound 3204

Compounds 3203 and 3204 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

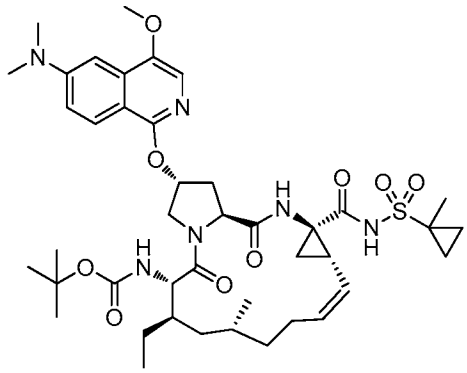
Compound 3203: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 876.6 (M^++1).

Compound 3204: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.10 (s, 1H), 7.87 (d, *J*=9.2 Hz, 1H), 7.65 (d, *J*=8.2 Hz, 1H), 7.11 (d, *J*=2.1 Hz, 1H), 6.86 (dd, *J*=9.0, 2.3 Hz, 1H), 6.57 (s, 1H), 5.77 (br. s., 1H), 5.61 - 5.48 (m, 1H), 5.12 (spt, *J*=6.2 Hz, 1H), 4.98 (t, *J*=9.9 Hz, 1H), 4.60 - 4.42 (m, 2H), 3.95 (dd, *J*=11.3, 3.4 Hz, 1H), 3.86 (s, 3H), 3.74 (dd, *J*=10.4, 8.5 Hz, 1H), 2.77 - 2.67 (m, 1H), 2.62 (dd, *J*=13.4, 7.3 Hz, 1H), 2.42 - 2.24 (m, 2H), 2.01 - 1.79 (m, 2H), 1.75 - 1.05 (m, 26H), 0.92 (dd, *J*=16.5, 6.7 Hz, 8H), 0.76 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 876.6 (M^++1).

Preparation of Compound 3205 and Compound 3206



Compound 3205



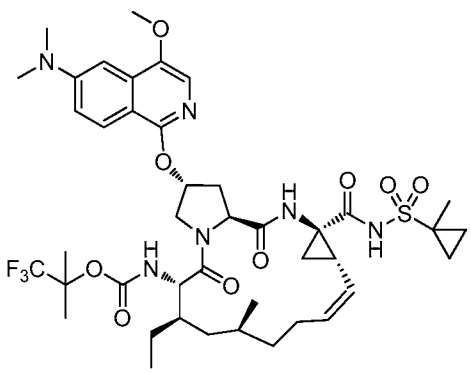
Compound 3206

Compounds 3205 and 3206 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

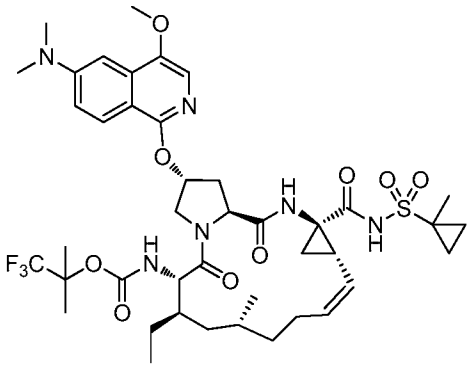
Compound 3205: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 825.5 (M^++1).

Compound 3206: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s, 1H), 9.09 (br. s., 1H), 7.89 (d, *J*=9.2 Hz, 1H), 7.45 (s, 1H), 7.20 (d, *J*=9.2 Hz, 1H), 7.09 (dd, *J*=9.3, 2.3 Hz, 1H), 6.92 (d, *J*=2.4 Hz, 1H), 5.74 (br. s., 1H), 5.61 - 5.46 (m, 1H), 4.97 (t, *J*=9.8 Hz, 1H), 4.53 (d, *J*=10.7 Hz, 1H), 4.48 - 4.37 (m, 1H), 4.03 - 3.87 (m, 5H), 3.09 - 3.02 (m, 6H), 2.79 - 2.55 (m, 2H), 2.44 - 2.19 (m, 2H), 2.04 - 1.84 (m, 2H), 1.68 - 0.68 (m, 31H); MS: MS *m/z* 825.5 (M^++1).

Preparation of Compound 3207 and Compound 3208



Compound 3207



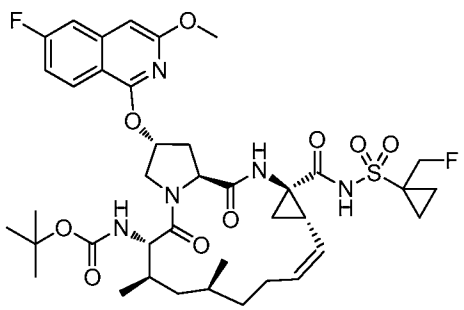
Compound 3208

Compounds 3207 and 3208 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

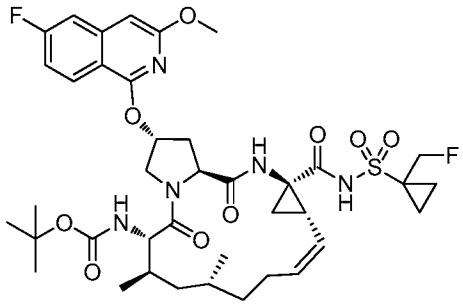
Compound 3207: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 879.6 (M^++1).

Compound 3208: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.13 (s, 1H), 7.86 (d, *J*=9.2 Hz, 2H), 7.46 (s, 1H), 7.12 (dd, *J*=9.3, 2.6 Hz, 1H), 6.92 (d, *J*=2.4 Hz, 1H), 5.75 (br. s., 1H), 5.61 - 5.47 (m, 1H), 4.98 (t, *J*=9.9 Hz, 1H), 4.57 - 4.40 (m, 2H), 3.99 - 3.86 (m, 5H), 3.10 - 3.00 (m, 6H), 2.78 - 2.65 (m, 1H), 2.64 - 2.55 (m, 1H), 2.42 - 2.17 (m, 2H), 2.05 - 1.82 (m, 2H), 1.67 - 0.67 (m, 28H); MS: MS *m/z* 879.6 (M^++1).

Preparation of Compound 3209 and Compound 3210



Compound 3209



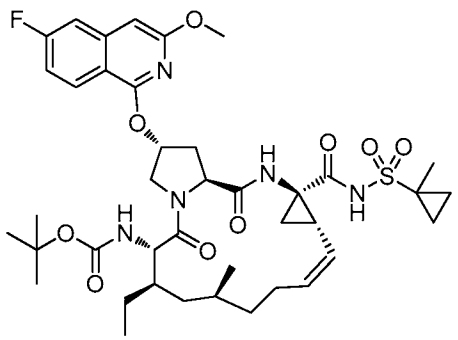
Compound 3210

Compounds 3209 and 3210 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

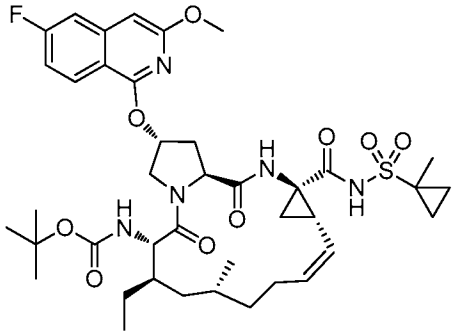
Compound 3209: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 804.5 (M^++1).

Compound 3210: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.04 (br. s., 1H), 8.07 (dd, *J*=8.9, 5.8 Hz, 1H), 7.53 (d, *J*=10.4 Hz, 1H), 7.26 - 7.10 (m, 2H), 6.71 (s, 1H), 5.80 (br. s., 1H), 5.58 - 5.46 (m, 1H), 4.99 (t, *J*=9.9 Hz, 1H), 4.91 - 4.72 (m, 1H), 4.70 - 4.42 (m, 3H), 3.99 - 3.87 (m, 4H), 3.77 - 3.66 (m, 1H), 2.74 - 2.59 (m, 2H), 2.41 - 2.22 (m, 2H), 1.97 - 1.76 (m, 2H), 1.73 - 1.63 (m, 1H), 1.61 - 1.03 (m, 18H), 0.99 - 0.84 (m, 6H), 0.74 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 804.5 (M^++1).

Preparation of Compound 3211 and Compound 3212



Compound 3211



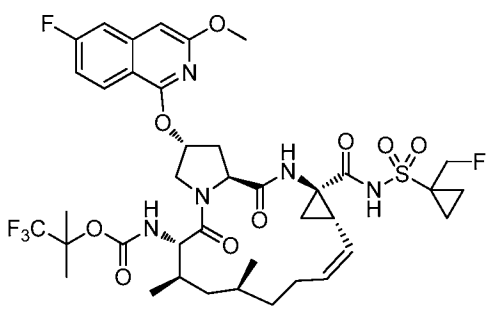
Compound 3212

Compounds 3211 and 3212 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

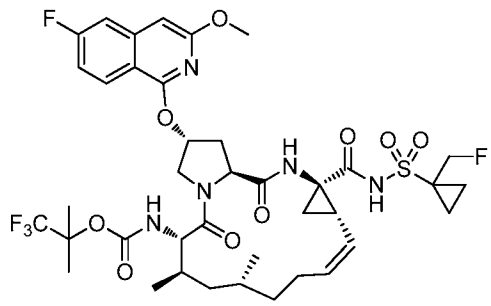
Compound 3211: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 800.5 (M^++1).

Compound 3212: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.11 (br. s., 1H), 8.05 (dd, *J*=9.0, 6.0 Hz, 1H), 7.53 (dd, *J*=10.4, 2.4 Hz, 1H), 7.21 (d, *J*=8.9 Hz, 1H), 7.16 (td, *J*=8.9, 2.4 Hz, 1H), 6.72 (s, 1H), 5.82 (br. s., 1H), 5.62 - 5.47 (m, 1H), 5.05 - 4.92 (m, 1H), 4.64 (d, *J*=11.3 Hz, 1H), 4.55 - 4.43 (m, 1H), 4.01 - 3.85 (m, 5H), 2.80 - 2.60 (m, 2H), 2.42 - 2.25 (m, 2H), 2.02 - 1.85 (m, 2H), 1.69 - 0.67 (m, 31H); MS: MS *m/z* 800.5 (M^++1).

Preparation of Compound 3213 and Compound 3214



Compound 3213



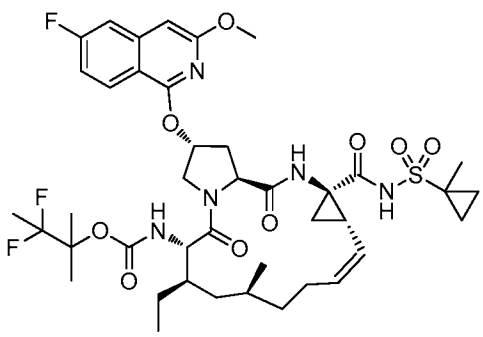
Compound 3214

Compounds 3213 and 3214 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

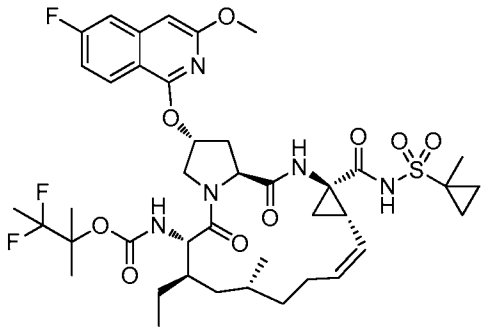
Compound 3213: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 858.6 (M^++1).

Compound 3214: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (s, 1H), 9.07 (s, 1H), 8.05 (dd, *J*=9.2, 5.8 Hz, 1H), 7.84 (d, *J*=7.6 Hz, 1H), 7.55 (dd, *J*=10.4, 2.4 Hz, 1H), 7.21 (td, *J*=8.9, 2.4 Hz, 1H), 6.72 (s, 1H), 5.81 (br. s., 1H), 5.60 - 5.45 (m, 1H), 5.00 (t, *J*=9.8 Hz, 1H), 4.91 - 4.71 (m, 1H), 4.66 - 4.45 (m, 3H), 3.97 - 3.90 (m, 4H), 3.70 (dd, *J*=10.7, 7.9 Hz, 1H), 2.70 - 2.60 (m, 2H), 2.41 - 2.24 (m, 2H), 1.96 - 1.78 (m, 2H), 1.74 - 1.64 (m, 1H), 1.62 - 1.04 (m, 15H), 0.97 - 0.86 (m, 6H), 0.76 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 858.7 (M^++1).

Preparation of Compound 3215 and Compound 3216



Compound 3215



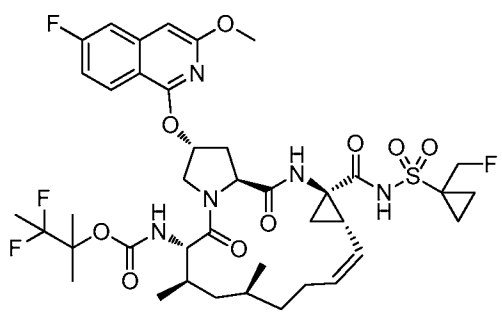
Compound 3216

Compounds 3215 and 3216 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

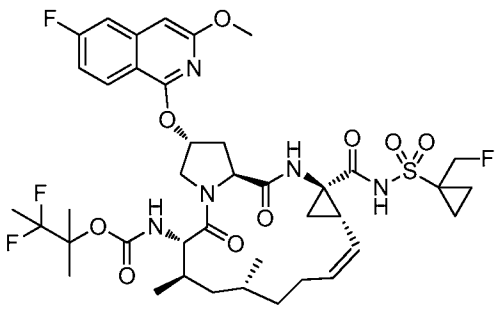
Compound 3215: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 850.7 (M^++1).

Compound 3216: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.12 (br. s., 1H), 8.03 (dd, *J*=9.2, 5.8 Hz, 1H), 7.66 (d, *J*=8.5 Hz, 1H), 7.55 (dd, *J*=10.4, 2.4 Hz, 1H), 7.19 (td, *J*=8.9, 2.4 Hz, 1H), 6.73 (s, 1H), 5.82 (br. s., 1H), 5.62 - 5.48 (m, 1H), 5.10 - 4.91 (m, 1H), 4.58 (d, *J*=11.3 Hz, 1H), 4.52 (dd, *J*=9.9, 6.9 Hz, 1H), 3.97 (dd, *J*=11.4, 3.2 Hz, 1H), 3.94 - 3.87 (m, 4H), 2.76 - 2.61 (m, 2H), 2.43 - 2.28 (m, 2H), 2.00 - 1.88 (m, 2H), 1.70 - 0.84 (m, 28H), 0.75 (t, *J*=7.3 Hz, 3H); MS: MS *m/z* 850.6 (M^++1).

Preparation of Compound 3217 and Compound 3218



Compound 3217



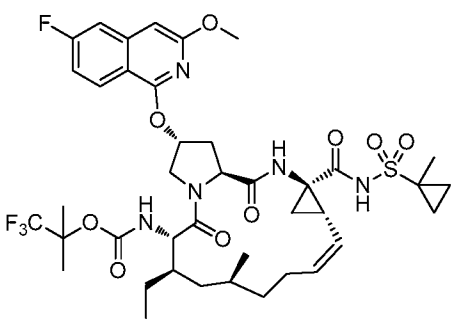
Compound 3218

Compounds 3217 and 3218 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

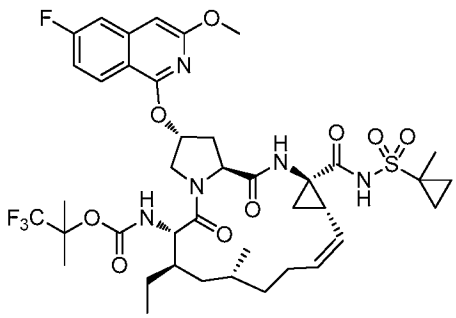
Compound 3217: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 854.7 (M^++1).

Compound 3218: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.04 (br. s., 1H), 8.05 (dd, *J*=9.0, 6.0 Hz, 1H), 7.62 (d, *J*=7.9 Hz, 1H), 7.55 (dd, *J*=10.5, 2.3 Hz, 1H), 7.19 (td, *J*=8.9, 2.4 Hz, 1H), 6.72 (s, 1H), 5.80 (br. s., 1H), 5.64 - 5.44 (m, 1H), 5.00 (t, *J*=9.3 Hz, 1H), 4.90 - 4.72 (m, 1H), 4.66 - 4.42 (m, 3H), 4.01 - 3.87 (m, 4H), 3.71 (dd, *J*=10.7, 8.2 Hz, 1H), 2.74 - 2.60 (m, 2H), 2.40 - 2.24 (m, 2H), 1.98 - 1.76 (m, 2H), 1.74 - 1.08 (m, 16H), 1.01 (s, 3H), 0.92 (dd, *J*=19.7, 6.6 Hz, 6H), 0.76 (t, *J*=11.6 Hz, 1H); MS: MS *m/z* 854.7 (M^++1).

Preparation of Compound 3219 and Compound 3220



Compound 3219



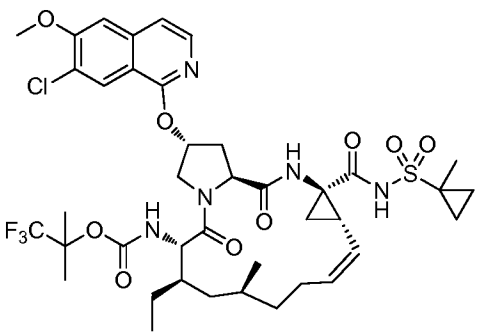
Compound 3220

Compounds 3219 and 3220 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

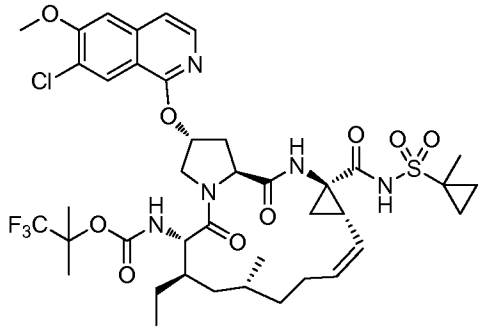
Compound 3219: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 854.7 (M^++1).

Compound 3220: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.14 (br. s., 1H), 8.03 (dd, *J*=9.2, 5.8 Hz, 1H), 7.88 (d, *J*=8.2 Hz, 1H), 7.55 (dd, *J*=10.5, 2.3 Hz, 1H), 7.21 (td, *J*=8.9, 2.4 Hz, 1H), 6.73 (s, 1H), 5.83 (br. s., 1H), 5.61 - 5.48 (m, 1H), 4.98 (t, *J*=9.5 Hz, 1H), 4.64 - 4.50 (m, 2H), 4.03 - 3.83 (m, 5H), 2.73 - 2.60 (m, 2H), 2.40 - 2.24 (m, 2H), 2.02 - 1.84 (m, 2H), 1.68 - 0.79 (m, 25H), 0.74 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 854.6 (M^++1).

Preparation of Compound 3221 and Compound 3222



Compound 3221



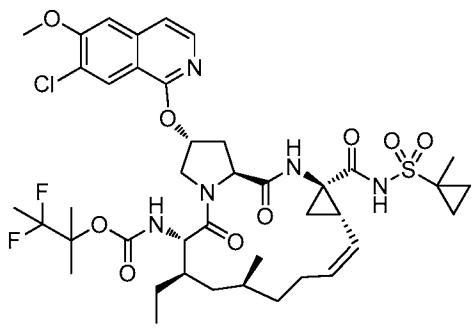
Compound 3222

Compounds 3221 and 3222 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

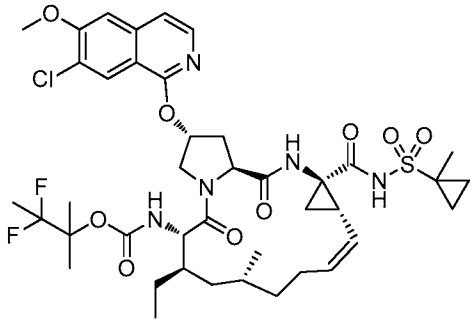
Compound 3221: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-chloro-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 870.7 (M^++1).

Compound 3222: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-chloro-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.00 (br. s., 1H), 9.12 (br. s., 1H), 8.06 - 7.96 (m, 2H), 7.84 (d, *J*=8.2 Hz, 1H), 7.52 (s, 1H), 7.36 (d, *J*=5.8 Hz, 1H), 5.86 (br. s., 1H), 5.58 - 5.44 (m, *J*=5.8 Hz, 1H), 5.04 - 4.92 (m, 1H), 4.62 - 4.46 (m, 2H), 3.99 (s, 3H), 3.93 (d, *J*=8.5 Hz, 1H), 3.85 (t, *J*=9.9 Hz, 1H), 2.74 - 2.57 (m, 2H), 2.39 - 2.24 (m, 2H), 2.00 - 1.82 (m, 2H), 1.66 - 0.75 (m, 25H), 0.71 (t, *J*=7.3 Hz, 3H); MS: MS *m/z* 870.6 (M^++1).

Preparation of Compound 3223 and Compound 3224



Compound 3223



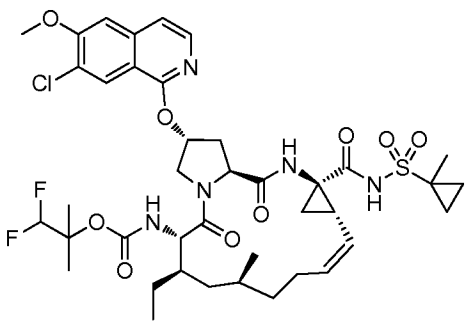
Compound 3224

Compounds 3223 and 3224 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

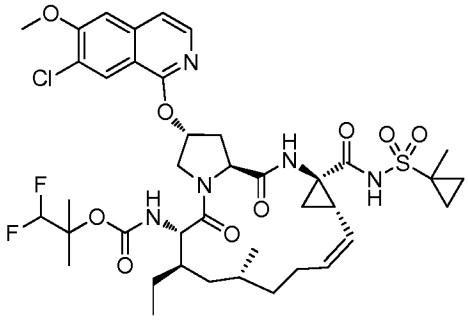
Compound 3223: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-chloro-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 866.7 (M^++1).

Compound 3224: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-chloro-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.11 (br. s., 1H), 8.06 - 7.97 (m, 2H), 7.61 (d, *J*=8.9 Hz, 1H), 7.53 (s, 1H), 7.36 (d, *J*=5.8 Hz, 1H), 5.86 (br. s., 1H), 5.59 - 5.45 (m, *J*=6.4 Hz, 1H), 5.08 - 4.93 (m, 1H), 4.63 - 4.46 (m, 2H), 3.99 (s, 3H), 3.97 - 3.80 (m, 2H), 2.77 - 2.57 (m, 2H), 2.32 (d, *J*=9.8 Hz, 2H), 1.91 (d, *J*=5.2 Hz, 2H), 1.67 - 0.67 (m, 31H); MS: MS *m/z* 866.8 (M^++1).

Preparation of Compound 3225 and Compound 3226



Compound 3225



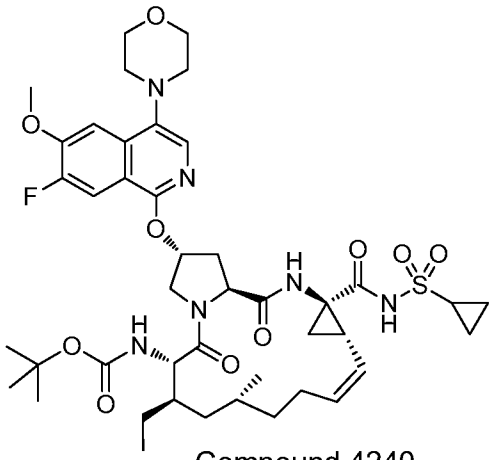
Compound 3226

Compounds 3225 and 3226 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 3225: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-chloro-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; MS: MS *m/z* 852.8 (M^++1).

Compound 3226: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-chloro-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.13 (br. s., 1H), 8.06 - 7.97 (m, 2H), 7.67 (d, *J*=8.5 Hz, 1H), 7.52 (s, 1H), 7.36 (d, *J*=5.8 Hz, 1H), 5.82 (br. s., 1H), 5.77 - 5.47 (m, 2H), 5.09 - 4.93 (m, 1H), 4.65 - 4.52 (m, 2H), 3.98 (s, 3H), 3.91 (d, *J*=8.9 Hz, 1H), 3.85 - 3.76 (m, 1H), 2.75 - 2.57 (m, 2H), 2.38 - 2.22 (m, 2H), 2.00 - 1.81 (m, 2H), 1.67 - 0.62 (m, 28H); MS: MS *m/z* 852.8 (M^++1).

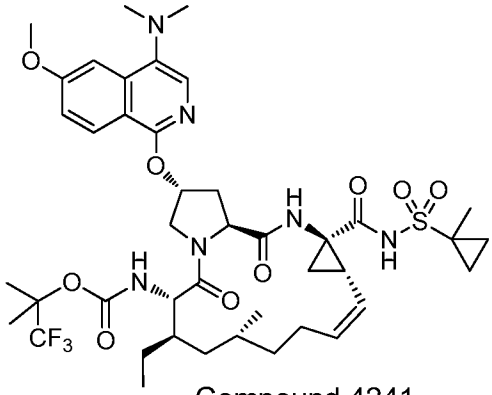
Preparation of Compound 4240



Compound 4240

Compound 4240 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001. Compound 4240: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-fluoro-6-methoxy-4-morpholinoisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.73 - 7.79 (m, 2 H) 7.59 (d, *J*=8.28 Hz, 1 H) 5.86 (br. s., 1 H) 5.60 - 5.67 (m, 1 H) 5.05 (t, *J*=9.91 Hz, 1 H) 4.75 (d, *J*=11.04 Hz, 1 H) 4.59 - 4.66 (m, 1 H) 4.02 - 4.11 (m, 5 H) 3.92 - 4.00 (m, 5 H) 3.10 (d, *J*=4.27 Hz, 5 H) 2.94 (t, *J*=4.77 Hz, 2 H) 2.68 - 2.77 (m, 3 H) 2.42 (br. s., 2 H) 1.96 (d, *J*=11.04 Hz, 3 H) 1.75 - 1.83 (m, 1 H) 1.51 - 1.64 (m, 6 H) 1.26 - 1.38 (m, 5 H) 0.99 - 1.20 (m, 9 H) 0.79 - 0.89 (m, 4 H); ^{19}F NMR: δ ppm -85.01 (1F). MS: MS *m/z* 871.7 (M^++1).

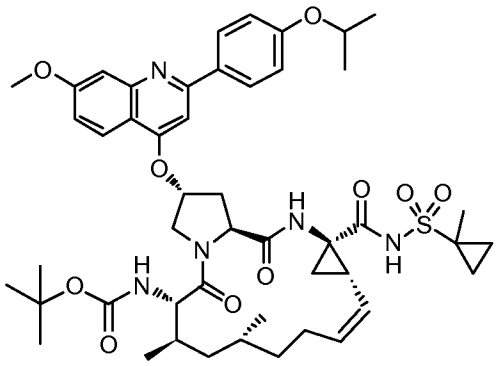
Preparation of Compound 4241



Compound 4241

Compound 4241 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4241: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17 (d, *J*=9.03 Hz, 1 H) 7.96 (s, 1 H) 7.45 (s, 1 H) 7.17 - 7.25 (m, 1 H) 5.89 (br. s., 1 H) 5.63 (d, *J*=5.77 Hz, 1 H) 4.97 - 5.04 (m, 1 H) 4.67 (d, *J*=10.04 Hz, 1 H) 3.99 - 4.08 (m, 6 H) 3.08 (s, 8 H) 2.68 - 2.77 (m, 3 H) 2.38 - 2.49 (m, 3 H) 1.94 - 2.03 (m, 3 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.67 (d, *J*=10.29 Hz, 2 H) 1.57 (dd, *J*=9.29, 5.27 Hz, 9 H) 1.40 - 1.46 (m, 2 H) 1.31 (br. s., 4 H) 1.13 (t, *J*=12.67 Hz, 1 H) 1.02 (d, *J*=6.78 Hz, 6 H) 0.81 - 0.91 (m, 4 H). ^{19}F NMR: δ ppm -84.98 (3F). MS: MS *m/z* 879.6 (M^++1).

Preparation of Compound 4242

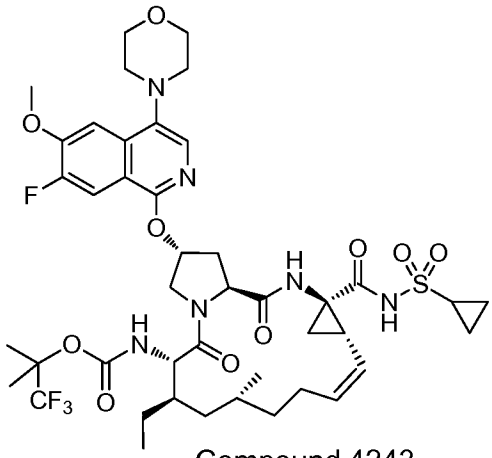


Compound 4242

Compound 4242 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4242: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2-(4-isopropoxyphenyl)-7-methoxyquinolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.31 (d, *J*=9.29 Hz, 1 H) 8.07 (d, *J*=9.03 Hz, 2 H) 7.61 (s, 1 H) 7.52 (d, *J*=2.26 Hz, 1 H) 7.37 (dd, *J*=9.29, 2.51 Hz, 1 H) 7.15 - 7.30 (m, 2 H) 5.87 (br. s., 1 H) 5.64 (t, *J*=10.16, 5.77 Hz, 1 H) 4.94 - 5.08 (m, 1 H) 4.61 - 4.79 (m, 1 H) 4.15 (dd, *J*=12.05, 3.01 Hz, 1 H) 3.96 - 4.09 (m, 4 H) 3.82 (d, *J*=10.79 Hz, 1 H) 3.50 (t, *J*=1.63 Hz, 1 H) 3.35 - 3.40 (m, 1 H) 3.05 - 3.21 (m, 1 H) 2.90 (dd, *J*=13.93, 6.90 Hz, 1 H) 2.55 - 2.79 (m, 2 H) 2.43 (d, *J*=13.05 Hz, 1 H) 1.90 - 2.05 (m, 7 H) 1.76 - 1.90 (m, 12 H) 1.65 - 1.75 (m, 1 H) 1.59 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.53 - 1.56 (m, 1 H) 1.39 - 1.49 (m, 6 H) 1.15 - 1.39 (m, 2 H) 1.09 - 1.13 (m, 1 H) 0.98 - 1.07 (m, 5 H) 0.76 - 0.94 (m, 3 H). MS: MS *m/z* 902.4 (M^++1).

Preparation of Compound 4243

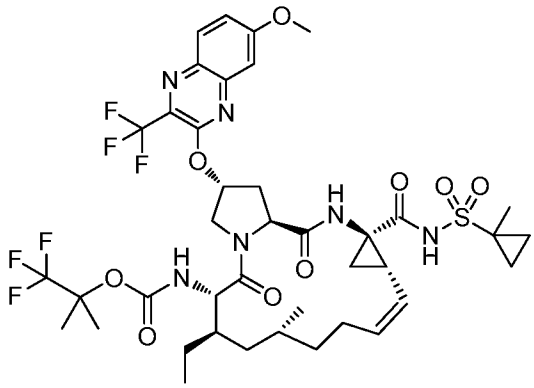


Compound 4243

Compound 4243 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4243: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-fluoro-6-methoxy-4-morpholinoisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.72 - 7.80 (m, 2 H) 7.60 (d, *J*=8.28 Hz, 1 H) 5.87 - 5.87 (m, 1 H) 5.82 - 5.88 (m, 1 H) 5.57 - 5.66 (m, 1 H) 5.04 (t, *J*=10.04 Hz, 1 H) 4.72 (d, *J*=11.54 Hz, 1 H) 4.64 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.03 - 4.08 (m, 4 H) 3.93 - 3.99 (m, 4 H) 3.06 - 3.11 (m, 4 H) 2.90 - 2.97 (m, 1 H) 2.67 - 2.78 (m, 4 H) 2.36 - 2.49 (m, 2 H) 1.93 - 2.04 (m, 2 H) 1.79 (dd, *J*=8.16, 5.65 Hz, 1 H) 1.59 (dd, *J*=9.41, 5.40 Hz, 4 H) 1.29 - 1.39 (m, 6 H) 0.98 - 1.16 (m, 12 H) 0.84 (t, *J*=7.28 Hz, 3 H). ^{19}F NMR: δ ppm -85.04 (3F) -134.37 (1F). MS: MS *m/z* 923.2 (M^{+}-1).

Preparation of Compound 4244

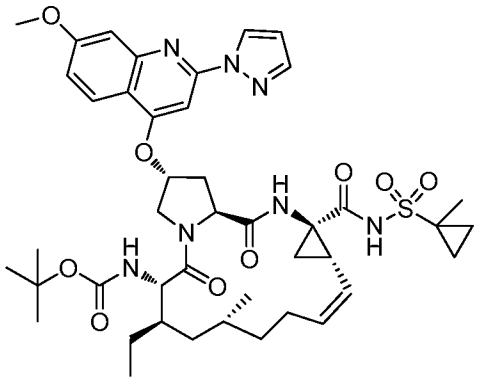


Compound 4244

Compound 4244 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4244: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm .99 (d, *J*=9.04 Hz, 1 H) 7.37 (m, 2 H) 6.01 (br. s., 1 H) 5.62 (br. s., 1 H) 5.00 (m, 1 H) 4.91 (s, 1 H) 4.80 (m, 1 H) 4.02 (m, 4 H) 3.40 (m, 1 H) 3.28 (dt, *J*=3.39, 1.57 Hz, 2 H) 2.70 (m, 2 H) 2.47 (m, 2 H) 2.00 (d, *J*=13.05 Hz, 2 H) 1.77 (m, 1 H) 1.67 (d, *J*=10.79 Hz, 1 H) 1.52 (m, 8 H) 1.25 (m, 6 H) 1.12 (m, 4 H) 1.01 (d, *J*=6.27 Hz, 2 H) 0.90 (br. s., 2 H) 0.80 (t, *J*=7.28 Hz, 2 H). ^{19}F NMR: δ ppm -68.71 (3F) -85.14 (3F). MS: MS *m/z* 905.8 (M^{+}+1).

Preparation of Compound 4245

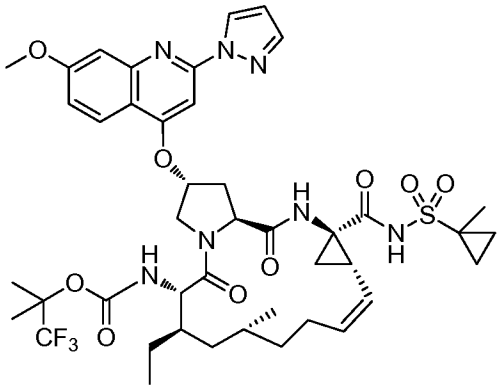


Compound 4245

Compound 4245 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4245: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-methoxy-2-(1H-pyrazol-1-yl)quinolin-4-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.04 (s, 1 H) 8.81 (d, *J*=2.64 Hz, 1 H) 8.08 (d, *J*=9.25 Hz, 1 H) 7.88 (s, 1 H) 7.57 (s, 1 H) 7.36 (d, *J*=2.17 Hz, 1 H) 6.97 - 7.15 (m, 1 H) 6.64 (s, 1 H) 5.63 (br. s., 2 H) 4.94 - 5.14 (m, 2 H) 4.50 - 4.70 (m, 1 H) 4.04 - 4.23 (m, 2 H) 3.97 (s, 3 H) 3.56 (t, *J*=3.28, 1.62 Hz, 1 H) 3.09 (d, *J*=3.28, 1.62 Hz, 1 H) 2.80 - 2.93 (m, 1 H) 2.73 (d, *J*=9.35 Hz, 1 H) 2.32 - 2.57 (m, 2 H) 1.90 - 2.08 (m, 2 H) 1.76 (dd, *J*=8.45, 5.71 Hz, 1 H) 1.52 - 1.66 (m, 6 H) 1.52 (s, 4 H) 1.43 (dd, *J*=9.63, 4.34 Hz, 2 H) 1.31 (s, 2 H) 1.18 (s, 5 H) 1.02 (d, *J*=6.52 Hz, 2 H) 0.76 - 0.94 (m, 3 H). MS: MS *m/z* 849.02 (M^++1).

Preparation of Compound 4246

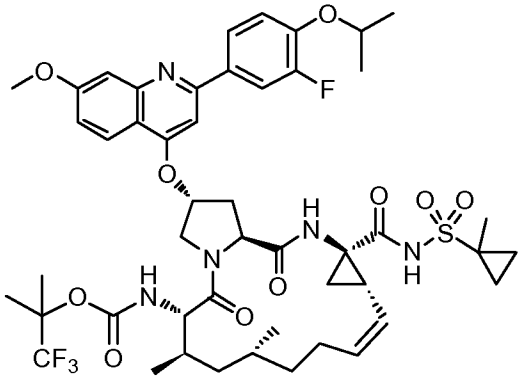


Compound 4246

Compound 4246 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4246: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-methoxy-2-(1H-pyrazol-1-yl)quinolin-4-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm8.80 (d, *J*=2.01 Hz, 1 H) 8.05 (d, *J*=9.03 Hz, 1 H) 7.86 (s, 1 H) 7.56 (s, 1 H) 7.29 - 7.42 (m, 2 H) 7.07 (dd, *J*=9.16, 2.38 Hz, 1 H) 6.48 - 6.72 (m, 1 H) 5.62 (br. s., 2 H) 4.94 - 5.12 (m, 1 H) 4.66 (dd, *J*=10.04, 7.28 Hz, 1 H) 4.02 - 4.26 (m, 2 H) 3.97 (s, 3 H) 3.50 (d, *J*=1.51 Hz, 1 H) 3.01 - 3.23 (m, 1 H) 2.84 (dd, *J*=14.30, 7.53 Hz, 1 H) 2.64 - 2.79 (m, 1 H) 2.39 - 2.60 (m, 1 H) 1.90 - 2.14 (m, 2 H) 1.77 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.56 - 1.71 (m, 4 H) 1.53 (s, 4 H) 1.37 - 1.47 (m, 3 H) 1.21 - 1.33 (m, 1 H) 1.14 - 1.23 (m, 1 H) 1.12 (s, 1 H) 1.02 (d, *J*=6.78 Hz, 2 H) 0.76 - 0.98 (m, 3 H). MS: MS *m/z* 902.4 (M^++1).

Preparation of Compound 4247

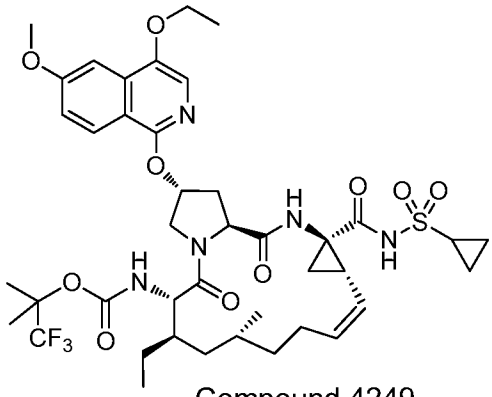


Compound 4247

Compound 4247 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4247: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2-(3-fluoro-4-isopropoxyphenyl)-7-methoxyquinolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.31 (d, *J*=9.29 Hz, 1 H) 8.07 (m, 2 H) 7.61 (m, 2 H)) 7.37 (t, *J*=9.29 Hz, 1 H) 7.15 - 7.30 (d, *J*=9.29 Hz, 1 H,) 5.87 (br. s., 1 H) 5.64 (t, *J*=10.16, 5.77 Hz, 1 H) 4.94 - 5.08 (m, 1 H) 4.61 - 4.79 (m, 1 H) 4.15 (dd, *J*=12.05, 3.01 Hz, 1 H) 3.96 - 4.09 (m, 2 H) 3.82 (d, *J*=10.79 Hz, 1 H) 3.50 (t, *J*=1.63 Hz, 1 H) 3.35 - 3.40 (m, 1 H) 3.05 - 3.21 (m, 1 H) 2.90 (dd, *J*=13.93, 6.90 Hz, 1 H) 2.55 - 2.79 (m, 2 H) 2.43 (d, *J*=13.05 Hz, 1 H) 1.90 - 2.05 (m, 11 H) 1.76 - 1.90 (m, 6 H) 1.65 - 1.75 (m, 1 H) 1.59 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.53 - 1.56 (m, 1 H) 1.39 - 1.49 (m, 6 H) 1.15 - 1.39 (m, 2 H) 1.09 - 1.13 (m, 1 H) 0.98 - 1.07 (m, 5 H) 0.76 - 0.94 (m, 3 H). MS: MS *m/z* 974.73 (M^++1).

Preparation of Compound 4249

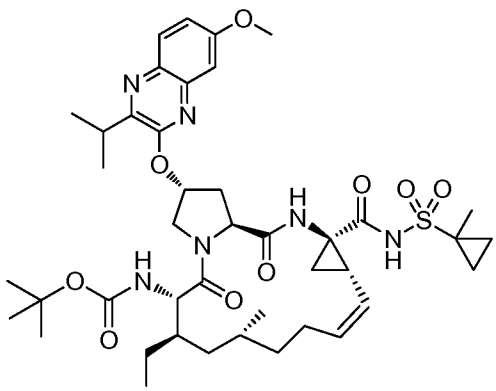


Compound 4249

Compound 4249 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4249: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-ethoxy-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.05 (d, *J*=9.03 Hz, 1 H) 7.53 (s, 1 H) 7.44 (d, *J*=2.51 Hz, 1 H) 7.28 (d, *J*=8.78 Hz, 1 H) 7.15 (dd, *J*=9.16, 2.64 Hz, 1 H) 5.81 (br. s., 1 H) 5.60 - 5.67 (m, 1 H) 5.04 (t, *J*=9.91 Hz, 2 H) 4.75 (s, 1 H) 4.64 (d, *J*=3.01 Hz, 1 H) 4.24 (q, *J*=7.03 Hz, 3 H) 4.03 - 4.10 (m, 2 H) 3.94 - 4.01 (m, 6 H) 2.94 (td, *J*=8.41, 4.02 Hz, 2 H) 2.69 - 2.77 (m, 3 H) 2.42 (ddd, *J*=13.80, 10.16, 4.14 Hz, 3 H) 1.94 - 2.02 (m, 2 H) 1.79 (dd, *J*=8.41, 5.65 Hz, 2 H) 1.51 - 1.61 (m, 7 H) 1.32 - 1.40 (m, 6 H) 1.14 - 1.25 (m, 3 H) 0.83 (t, *J*=7.40 Hz, 3 H). ^{19}F NMR: δ ppm -85.06 (3F). MS: MS *m/z* 866.7 (M^{+}+1).

Preparation of Compound 4250

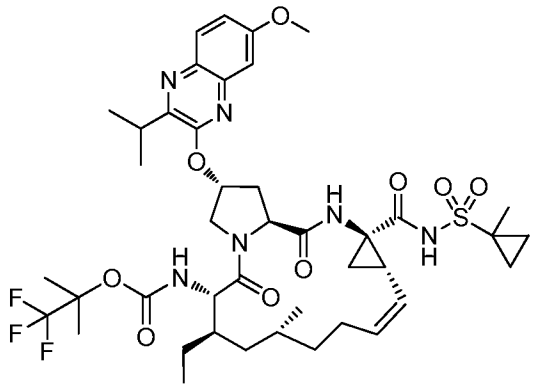


Compound 4250

Compound 4250 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001. Compound 4250: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate.

^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.11 (s, 1 H) 7.82 (d, *J*=9.03 Hz, 2 H) 7.23 (m, 3 H) 5.98 (br. s., 1 H) 5.63 (m, 1 H) 5.01 (t, *J*=9.91 Hz, 2 H) 4.62 (m, 3 H) 4.11 (d, *J*=11.04 Hz, 3 H) 3.96 (s, 5 H) 3.47 (m, 2 H) 2.72 (m, 3 H) 2.46 (m, 3 H) 1.99 (m, 3 H) 1.77 (dd, *J*=8.16, 5.65 Hz, 2 H) 1.66 (m, 2 H) 1.56 (m, 13 H) 1.38 (m, 16 H) 1.13 (m, 14 H) 1.01 (d, *J*=6.78 Hz, 5 H) 0.88 (m, 9 H). MS: MS *m/z* 825.69 (M^++1).

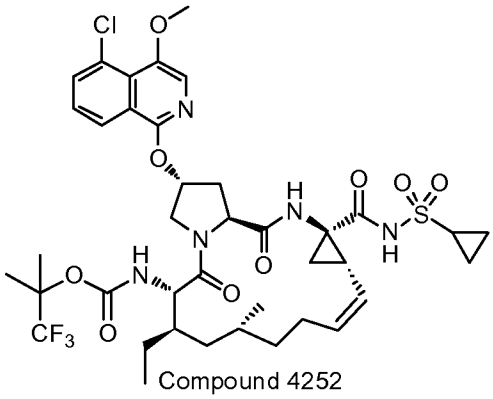
Preparation of Compound 4251



Compound 4251

Compound 4251 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001. Compound 4251: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.84 (d, *J*=9.29 Hz, 1 H) 7.29 (d, *J*=2.76 Hz, 1 H) 7.23 (dd, *J*=9.03, 2.76 Hz, 1 H) 5.96 (br. s., 1 H) 5.64 (m, 1 H) 5.02 (t, *J*=10.04 Hz, 2 H) 4.66 (m, 3 H) 4.09 (dd, *J*=11.54, 3.51 Hz, 3 H) 3.97 (s, 3 H) 3.44 (m, 4 H) 2.73 (m, 2 H) 2.48 (m, 2 H) 1.99 (m, 2 H) 1.78 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.67 (dd, *J*=9.54, 4.77 Hz, 1 H) 1.56 (m, 8 H) 1.37 (m, 14 H) 1.13 (m, 4 H) 1.02 (d, *J*=6.53 Hz, 3 H) 0.89 (m, 6 H). MS: MS *m/z* 879.72 (M^++1).

Preparation of Compound 4252

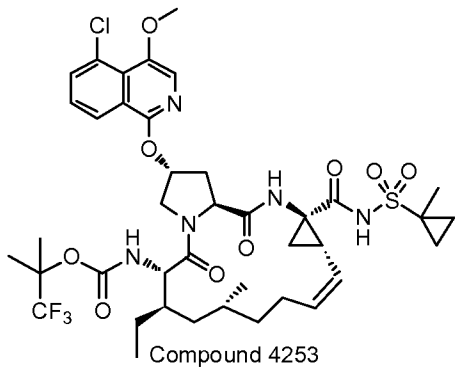


Compound 4252

Compound 4252 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3

Compound 4252: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.01 (s, 1 H) 8.17 (dd, *J*=8.28, 1.00 Hz, 2 H) 7.67 - 7.86 (m, 4 H) 7.48 (t, *J*=8.03 Hz, 2 H) 7.29 (d, *J*=8.53 Hz, 1 H) 5.85 (br. s., 2 H) 5.63 (t, *J*=10.23, 5.65 Hz, 2 H) 5.04 (t, *J*=9.91 Hz, 2 H) 4.77 (s, 1 H) 4.66 (dd, *J*=10.04, 7.03 Hz, 2 H) 3.89 - 4.11 (m, 5 H) 2.88 - 3.04 (m, 2 H) 2.68 - 2.84 (m, 4 H) 2.44 (dd, *J*=13.87, 4.02 Hz, 4 H) 1.89 - 2.11 (m, 4 H) 1.79 (dd, *J*=8.28, 5.52 Hz, 2 H) 1.44 - 1.74 (m, 5 H) 1.23 - 1.42 (m, 5 H) 1.03 - 1.23 (m, 6 H) 0.72 - 1.01 (m, 2 H). MS: MS *m/z* 856.2 (M^++1).

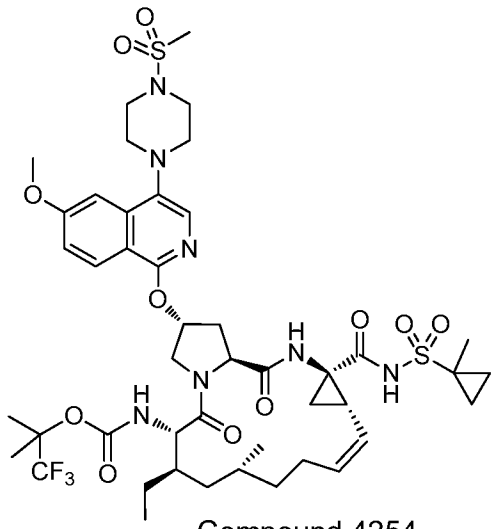
Preparation of Compound 4253



Compound 4253

Compound 4253 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3 Compound 4253:1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.17 (dd, *J*=8.28, 1.26 Hz, 1 H) 7.76 - 7.82 (m, 1 H) 7.73 (s, 1 H) 7.49 (d, *J*=8.03 Hz, 1 H) 5.85 (br. s., 1 H) 5.63 (d, *J*=6.02 Hz, 1 H) 5.01 (br. s., 1 H) 4.79 (d, *J*=12.05 Hz, 1 H) 4.67 (dd, *J*=10.16, 7.15 Hz, 1 H) 4.00 - 4.08 (m, 2 H) 3.96 - 3.99 (m, 3 H) 2.70 - 2.80 (m, 2 H) 2.45 (ddd, *J*=13.93, 10.16, 4.02 Hz, 2 H) 1.92 - 2.04 (m, 2 H) 1.78 (dd, *J*=8.28, 5.52 Hz, 1 H) 1.54 - 1.70 (m, 6 H) 1.40 - 1.47 (m, 2 H) 1.28 - 1.39 (m, 5 H) 1.05 - 1.20 (m, 2 H) 1.02 (d, *J*=6.53 Hz, 3 H) 0.87 - 0.95 (m, 5 H) 0.83 (s, 3 H). MS: MS *m/z* 871.9 (M^++1).

Preparation of Compound 4254

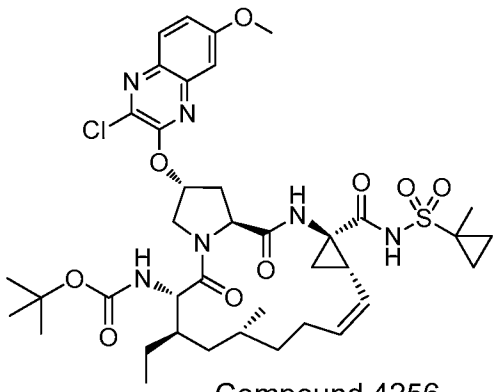


Compound 4254

Compound 4254 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4254: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-methoxy-4-(4-(methylsulfonyl)piperazin-1-yl)isoquinolin-1-yl)oxy)-9-methyl-14a-(((1-

methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.11 (d, *J*=9.29 Hz, 1 H) 7.75 (s, 1 H) 7.44 (s, 1 H) 7.15 (dd, *J*=9.03, 2.51 Hz, 1 H) 5.86 (br. s., 1 H) 5.63 (td, *J*=10.16, 5.77 Hz, 1 H) 4.99 - 5.03 (m, 1 H) 4.75 (d, *J*=11.54 Hz, 1 H) 4.65 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.05 (d, *J*=11.54 Hz, 2 H) 3.98 (s, 4 H) 3.63 - 3.67 (m, 1 H) 2.70 - 2.76 (m, 2 H) 2.39 - 2.46 (m, 2 H) 1.98 (t, *J*=11.92 Hz, 3 H) 1.77 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.64 - 1.69 (m, 2 H) 1.51 - 1.60 (m, 10 H) 1.41 - 1.47 (m, 2 H) 1.30 - 1.38 (m, 5 H) 1.08 - 1.18 (m, 2 H) 0.97 - 1.04 (m, 8 H) 0.80 - 0.90 (m, 7 H). ^{19}F NMR: δ ppm -85.01 (3F). MS: MS *m/z* 996.2 (M^++1).

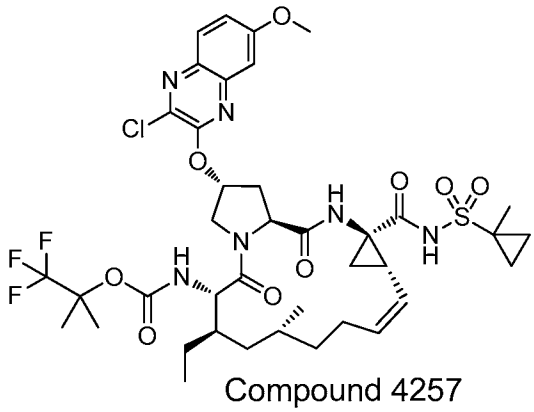
Preparation of Compound 4256



Compound 4256

Compound 4256 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001. Compound 4256: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-chloro-7-methoxyquinoxalin-2-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 815.2 (M^++1).

Preparation of Compound 4257

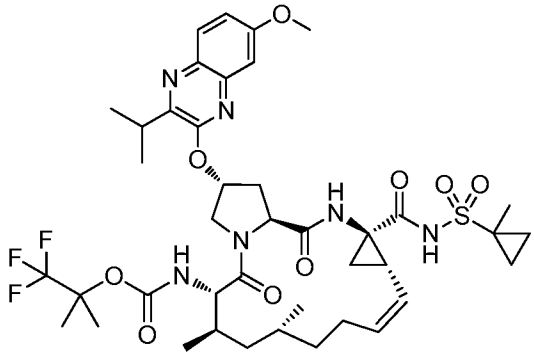


Compound 4257

Compound 4257 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4257: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-chloro-7-methoxyquinoxalin-2-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.13 (s, 1 H) 7.79 (d, *J*=9.03 Hz, 2 H) 5.93 (br. s., 2 H) 5.63 (td, *J*=10.16, 6.02 Hz, 2 H) 5.01 (t, *J*=10.04 Hz, 2 H) 4.81 (m, 2 H) 4.68 (dd, *J*=9.79, 7.03 Hz, 2 H) 4.06 (dd, *J*=11.67, 3.39 Hz, 2 H) 3.97 (m, 3 H) 2.73 (m, 2 H) 2.46 (m, 2 H) 1.98 (m, 2 H) 1.77 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.67 (m, 1 H) 1.50 (m, 8 H) 1.26 (m, 5 H) 1.12 (t, *J*=12.05 Hz, 1 H) 1.01 (d, *J*=6.78 Hz, 2 H) 0.90 (m, 2 H) 0.81 (t, *J*=7.53 Hz, 2 H). ^{19}F NMR: δ ppm -85.07 (3F). MS: MS *m/z* 869.2 (M^{+}-1).

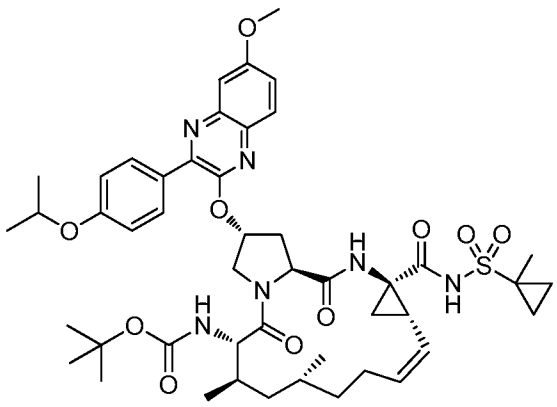
Preparation of Compound 4259



Compound 4259

Compound 4259 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4259: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.13 (s, 1 H) 7.83 (d, *J*=9.03 Hz, 1 H) 7.27 (d, *J*=2.76 Hz, 1 H) 7.22 (dd, *J*=9.03, 3.01 Hz, 1 H) 5.94 (br. s., 1 H) 5.63 (td, *J*=10.29, 5.52 Hz, 1 H) 5.01 (t, *J*=9.91 Hz, 1 H) 4.65 (m, 2 H) 4.09 (dd, *J*=11.80, 3.51 Hz, 1 H) 3.95 (m, 3 H) 3.85 (d, *J*=10.79 Hz, 1 H) 3.44 (quin, *J*=6.90 Hz, 1 H) 2.73 (m, 2 H) 2.46 (m, 2 H) 1.93 (m, 2 H) 1.79 (m, 2 H) 1.66 (m, 1 H) 1.55 (m, 5 H) 1.43 (m, 3 H) 1.34 (m, 10 H) 1.22 (m, 4 H) 0.99 (dd, *J*=17.57, 6.78 Hz, 6 H) 0.88 (m, 4 H). ^{19}F NMR: δ ppm -85.07 (3F). MS: MS *m/z* 865.2 (M^++1).

Preparation of Compound 4260

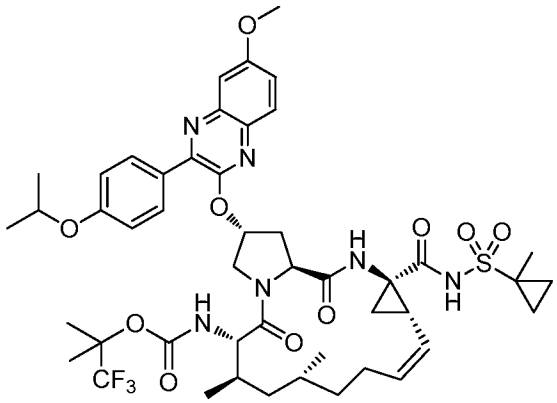


Compound 4260

Compound 4260 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001. Compound 4260: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(4-isopropoxyphenyl)-6-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-

a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.98 (d, *J*=8.78 Hz, 3 H) 7.79 (d, *J*=9.29 Hz, 1 H) 7.32 - 7.44 (m, 3 H) 7.02 (d, *J*=8.78 Hz, 3 H) 6.03 (br. s., 1 H) 4.74 (dt, *J*=12.11, 6.12 Hz, 3 H) 4.56 (d, *J*=7.78 Hz, 2 H) 4.10 (d, *J*=9.29 Hz, 1 H) 3.96 (s, 4 H) 3.79 - 3.86 (m, 1 H) 2.64 (dd, *J*=13.55, 7.28 Hz, 2 H) 2.45 (d, *J*=14.31 Hz, 3 H) 1.99 (br. s., 1 H) 1.71 - 1.89 (m, 4 H) 1.46 - 1.59 (m, 8 H) 1.29 - 1.37 (m, 5 H) 0.95 - 1.07 (m, 20 H). MS: MS *m/z* 903.86 (M^++1).

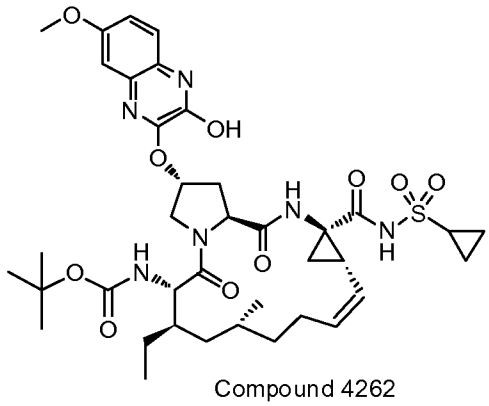
Preparation of Compound 4261



Compound 4261

Compound 4261 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4261: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(4-isopropoxyphenyl)-6-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.93 - 8.03 (m, 2 H) 7.81 (d, *J*=9.04 Hz, 1 H) 7.34 - 7.47 (m, 3 H) 6.97 - 7.09 (m, 2 H) 6.04 (br. s., 1 H) 5.64 (d, *J*=4.52 Hz, 1 H) 4.63 (dd, *J*=10.04, 7.28 Hz, 1 H) 4.08 (d, *J*=8.28 Hz, 1 H) 3.92 - 4.02 (m, 4 H) 3.79 - 3.88 (m, 1 H) 2.61 - 2.78 (m, 3 H) 2.41 - 2.52 (m, 2 H) 1.62 - 1.72 (m, 2 H) 1.45 - 1.57 (m, 6 H) 1.38 (dd, *J*=6.02, 4.27 Hz, 8 H) 1.16 - 1.28 (m, 4 H) 0.93 - 1.07 (m, 11 H). ^{19}F NMR: δ ppm -85.11 (1F). MS: MS *m/z* 957.78 (M^++1).

Preparation of Compound 4262

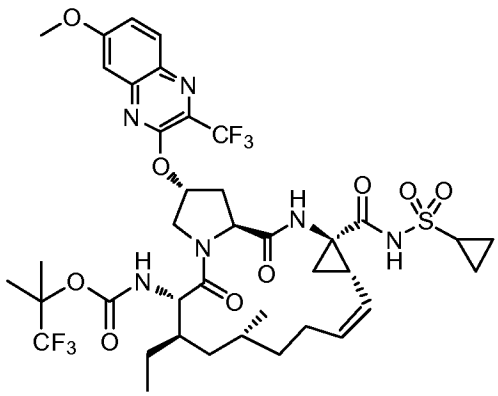


Compound 4262

Compound 4262 was prepared using 3-chloro-6-methoxy-2-(trifluoromethyl)quinoxaline and the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4262: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-hydroxy-7-methoxyquinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 12.24 (s, 1 H) 11.19 (s, 1 H) 9.07 (s, 1 H) 6.84 - 7.39 (m, 4 H) 5.69 (br. s., 1 H) 5.36 - 5.61 (m, 1 H) 5.02 (t, *J*=9.91 Hz, 1 H) 4.28 - 4.61 (m, 2 H) 3.58 - 4.08 (m, 4 H) 2.87 - 3.04 (m, 1 H) 2.63 - 2.82 (m, 1 H) 2.17 - 2.41 (m, 2 H) 1.63 (dd, *J*=8.28, 5.27 Hz, 1 H) 1.33 - 1.57 (m, 11 H) 1.07 - 1.24 (m, 11 H) 0.90 - 1.07 (m, 6 H) 0.60 - 0.82 (m, 3 H). MS: MS *m/z* 785.68 (M^++1).

Preparation of Compound 4263

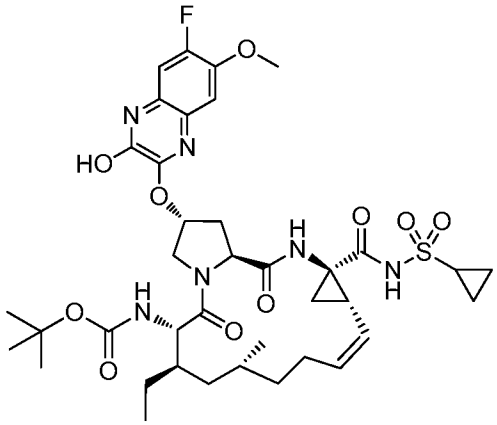


Compound 4263

Compound 4263 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3

Compound 4263: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.88 - 8.07 (m, 1 H) 7.28 - 7.47 (m, 2 H) 6.00 (br. s., 1 H) 5.61 (d, *J*=6.02 Hz, 1 H) 4.76 - 4.82 (m, 1 H) 4.47 - 4.68 (m, 1 H) 3.89 - 4.14 (m, 5 H) 2.63 - 2.79 (m, 1 H) 2.35 - 2.60 (m, 2 H) 1.88 - 2.10 (m, 3 H) 1.69 - 1.84 (m, 1 H) 1.41 - 1.65 (m, 5 H) 1.29 - 1.40 (m, 7 H) 1.23 - 1.29 (m, 4 H) 1.19 (s, 3 H) 1.07 - 1.16 (m, 2 H) 1.02 (d, *J*=6.78 Hz, 4 H) 0.71 - 0.94 (m, 4 H). MS: MS *m/z* 891.2 (M^++1).

Preparation of Compound 4265



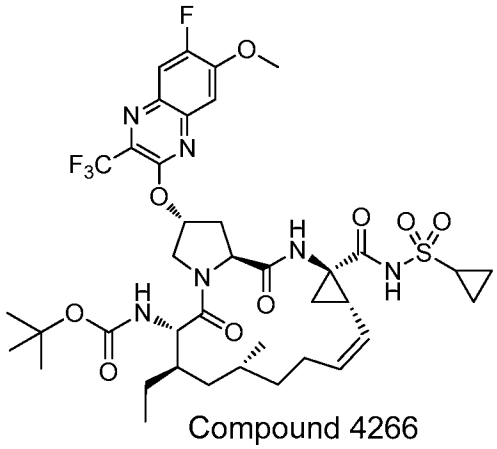
Compound 4265

Compound 4265 was isolated as by-product in the preparation of compound 4266. The intermediate was used in the synthesis 2-chloro-6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxaline.

Compound 4265: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((6-fluoro-3-hydroxy-7-methoxyquinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.35 (d, *J*=7.03 Hz, 1 H) 7.01 (d, *J*=11.04 Hz, 1 H) 5.76 (br. s., 1 H) 5.54 (br. s., 1 H)

4.94 (m, 2 H) 4.81 (m, 2 H) 4.64 (t, *J*=8.28 Hz, 1 H) 4.58 (s, 1 H) 4.15 (s, 1 H) 4.02 (d, *J*=11.04 Hz, 2 H) 3.96 (s, 4 H) 3.76 (m, 1 H) 3.38 (m, 3 H) 3.28 (m, 1 H) 3.16 (dt, *J*=3.14, 1.69 Hz, 1 H) 3.05 (m, 1 H) 2.51 (m, 7 H) 1.92 (m, 4 H) 1.43 (m, 10 H) 1.17 (s, 11 H) 1.00 (m, 9 H) 0.82 (t, *J*=7.53 Hz, 4 H). ^{19}F NMR: δ ppm -134.97 (1F). MS: MS *m/z* 801.2 (M^++1).

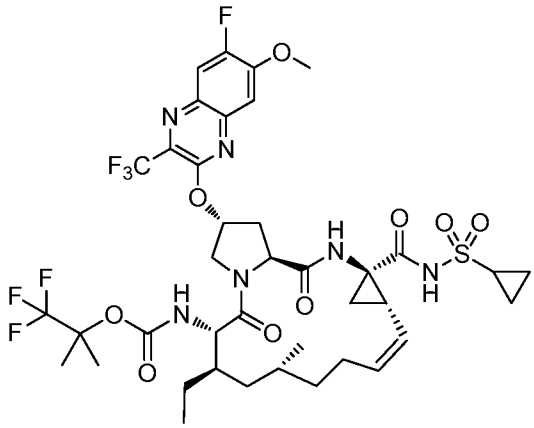
Preparation of Compound 4266



Compound 4266

Compound 4266 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001. Compound 4266: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm .77 (d, *J*=11.04 Hz, 1 H) 7.56 (d, *J*=8.53 Hz, 1 H) 5.99 (br. s., 1 H) 5.63 (td, *J*=10.23, 6.15 Hz, 1 H) 5.05 (t, *J*=9.79 Hz, 1 H) 4.93 (m, 2 H) 4.81 (m, 2 H) 4.63 (dd, *J*=9.79, 7.03 Hz, 1 H) 4.14 (m, 3 H) 4.03 (m, 2 H) 3.39 (m, 4 H) 3.28 (dt, *J*=3.26, 1.63 Hz, 1 H) 2.94 (m, 1 H) 2.71 (m, 2 H) 2.47 (m, 2 H) 1.97 (m, 2 H) 1.78 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.54 (m, 7 H) 1.31 (m, 3 H) 1.09 (m, 16 H) 0.87 (m, 4 H). ^{19}F NMR: δ ppm -68.82 (3F) -131.61 (1F). MS: MS *m/z* 853.2 (M^++1).

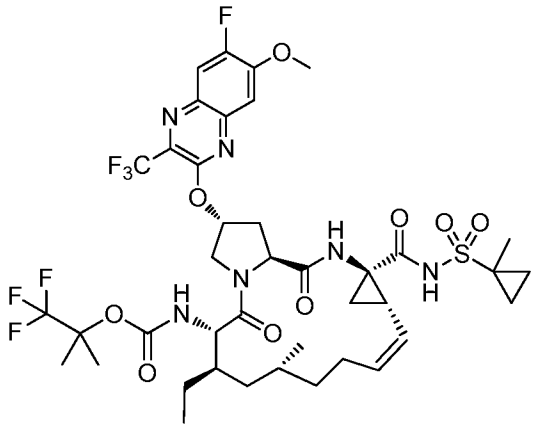
Preparation of Compound 4267



Compound 4267

Compound 4267 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4267: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.79 (d, *J*=11.04 Hz, 1 H) 7.57 (d, *J*=8.53 Hz, 1 H) 5.99 (br. s., 1 H) 5.62 (s, 1 H) 5.05 (s, 1 H) 4.63 (dd, *J*=10.04, 7.03 Hz, 1 H) 3.92 - 4.07 (m, 2 H) 4.13 (s, 3 H) 2.87 - 3.00 (m, 1 H) 2.65 - 2.78 (m, 3 H) 2.49 (s, 2 H) 1.98 (br. s., 2 H) 1.74 - 1.83 (m, 1 H) 1.43 - 1.68 (m, 7 H) 1.23 - 1.39 (m, 9 H) 1.01 - 1.16 (m, 8 H) 0.76 - 0.86 (m, 3 H). ^{19}F NMR: δ ppm -68.84 (3F) -85.10 (3F) -131.31 (1F). MS: MS *m/z* 854.91 (M^{+}+1).

Preparation of Compound 4268

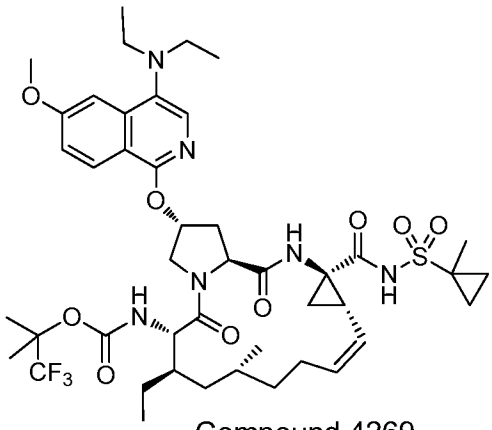


Compound 4268

Compound 4268 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4268: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.80 (d, *J*=11.04 Hz, 1 H) 7.58 (d, *J*=8.4 Hz, 1 H) 6.0 (br. s., 1 H) 5.63 (m, 1 H) 5.03 (m, 1 H) 4.66-4.64 (m, 2 H) 4.13 (s, 3H) 4.0 (m, 2 H) 2.76 (m, 3 H) 2.5 (m, 2 H) 1.9 (m, 2 H) 1.85-1.70 (m, 2 H) 1.62 - 1.50 (m, 11 H) 1.52 - 1.30 (m, 8 H) 1.2 - 1.12 (m, 1 H) 0.95 - 0.70 (m, 9 H). ^{19}F NMR: δ ppm -68.83 (3F) -85.10 (3F) -131.39 (1F). MS: MS *m/z* 921.2 (M^{+}-1).

Preparation of Compound 4269

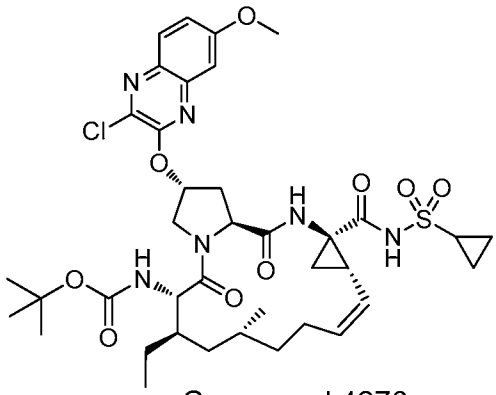


Compound 4269

Compound 4269 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4269 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-(diethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.23 (d, *J*=9.04 Hz, 2 H) 7.54 (br. s., 1 H) 7.29 (br. s., 1 H) 5.98 (br. s., 1 H) 5.64 (td, *J*=10.04, 6.27 Hz, 1 H) 5.02 (t, *J*=10.04 Hz, 2 H) 4.65 - 4.76 (m, 3 H) 4.00 - 4.08 (m, 4 H) 3.67 (br. s., 4 H) 2.70 - 2.80 (m, 3 H) 2.42 - 2.50 (m, 2 H) 1.96 - 2.04 (m, 2 H) 1.76 - 1.82 (m, 1 H) 1.64 - 1.69 (m, 1 H) 1.52 - 1.59 (m, 4 H) 1.40 - 1.46 (m, 2 H) 1.30 (br. s., 5 H) 1.12 - 1.19 (m, 6 H) 1.02 (d, *J*=6.53 Hz, 8 H) 0.81 - 0.92 (m, 6 H). MS: MS *m/z* 907.4 (M^++1).

Preparation of Compound 4270

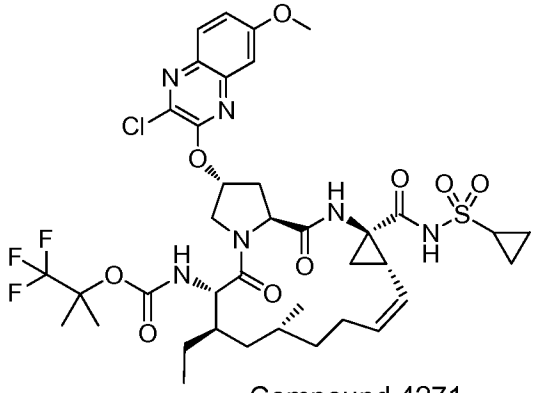


Compound 4270

Compound 4270 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001.

Compound 4270: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-chloro-7-methoxyquinoxalin-2-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.78 (d, *J*=9.29 Hz, 1 H) 7.35 (m, 2 H) 6.64 (m, 1 H) 5.92 (br. s., 1 H) 5.63 (td, *J*=10.10, 5.90 Hz, 1 H) 5.05 (m, 1 H) 4.87-4.64 (m, 2 H) 4.12-3.90 (m, 6 H) 2.9 (m, 1 H) 2.8 (m, 2 H) 2.4 (m, 2 H) 2.05-1.90 (m,3 H) 1.82-1.70 (m, 1 H) 1.72-1.5 (m, 8 H) 1.42-1.2 (m, 4 H) 1.22-1.10 (m, 14 H) 0.95-0.75 (m, 8 H). MS: MS *m/z* 855.2 (M^+-1).

Preparation of Compound 4271

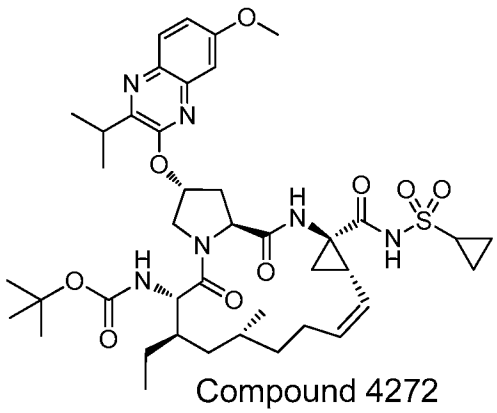


Compound 4271

Compound 4271 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4271: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-chloro-7-methoxyquinoxalin-2-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.09 (s, 1 H) 7.80 (d, *J*=9.29 Hz, 1 H) 7.36 (d, *J*=2.51 Hz, 1 H) 7.31 (m, 2 H) 5.92 (br. s., 1 H) 5.63 (td, *J*=10.10, 5.90 Hz, 2 H) 5.05 (t, *J*=9.91 Hz, 2 H) 4.91 (s, 1 H) 4.81 (m, 3 H) 4.68 (dd, *J*=9.91, 7.15 Hz, 2 H) 4.05 (dd, *J*=11.67, 3.39 Hz, 2 H) 3.99 (s, 4 H) 3.96 (s, 1 H) 3.38 (m, 4 H) 3.28 (dt, *J*=3.26, 1.63 Hz, 1 H) 2.95 (m, 2 H) 2.73 (m, 4 H) 2.46 (m, 4 H) 1.98 (t, *J*=11.67 Hz, 3 H) 1.79 (dd, *J*=8.41, 5.65 Hz, 2 H) 1.56 (m, 11 H) 1.33 (m, 14 H) 1.10 (m, 12 H) 0.84 (m, 6 H). MS: MS *m/z* 855.2 (M^+-1).

Preparation of Compound 4272

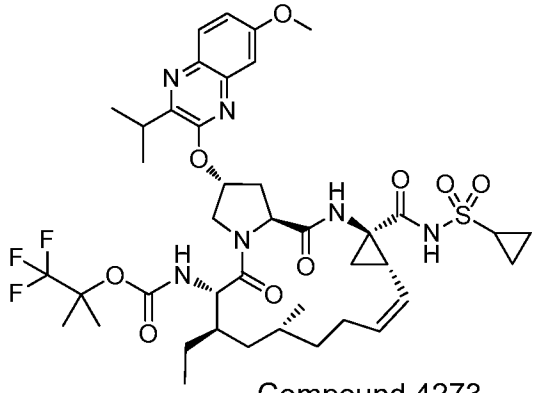


Compound 4272

Compound 4272 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001. Compound 4272: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.83 (d, *J*=8.8 Hz, 1 H) 7.27 -7.19 (m, 2 H) 6.68 (d, *J*=9.2, 1 H) 5.96 (br. s., 1 H) 5.66-5.59 (m, 1 H) 5.04 (t, *J*=10.04 Hz, 1 H) 4.69-4.58 (m, 2 H) 4.13-4.06 (m, 2 H) 3.95 (s, 3 H) 3.5- 3.43 (m, 1 H) 2.94 (tt, *J*=8.00, 4.80 Hz, 1 H) 2.75-2.68 (m, 2 H) 2.45 (m, 2 H) 1.98-1.95 (m, 2 H) 1.78 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.61-1.45 (m, 8 H) 1.35-1.28 (m, 11 H) 1.15-1.07 (m, 14 H)

1.07-095 (m, 5 H) 0.85-0.81 (m, 4 H). MS: MS *m/z* 865.2 (M^+-1).

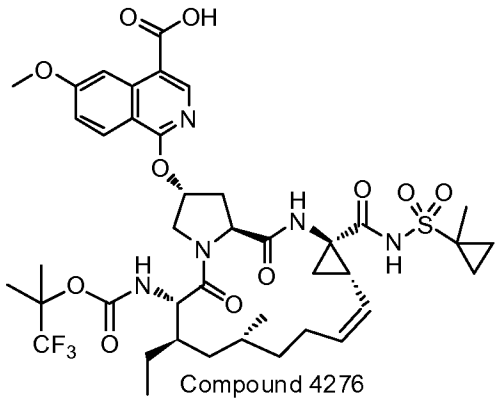
Preparation of Compound 4273



Compound 4273

Compound 4273 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4273: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.83 (d, *J*=9.03 Hz, 1 H) 7.28 (d, *J*=2.76 Hz, 1 H) 7.22 (dd, *J*=9.03, 2.76 Hz, 1 H) 5.94 (br. s., 1 H) 5.63 (td, *J*=10.16, 5.77 Hz, 1 H) 5.04 (t, *J*=10.04 Hz, 1 H) 4.64 (m, 2 H) 4.07 (m, 2 H) 3.95 (m, 3 H) 3.47 (m, 1 H) 2.94 (tt, *J*=8.00, 4.80 Hz, 1 H) 2.72 (m, 2 H) 2.45 (m, 2 H) 2.01 (m, 2 H) 1.78 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.53 (m, 7 H) 1.30 (m, 12 H) 1.09 (m, 10 H). ^{19}F NMR: δ ppm -85.06 (3F). MS: MS *m/z* 865.2 (M^+-1).

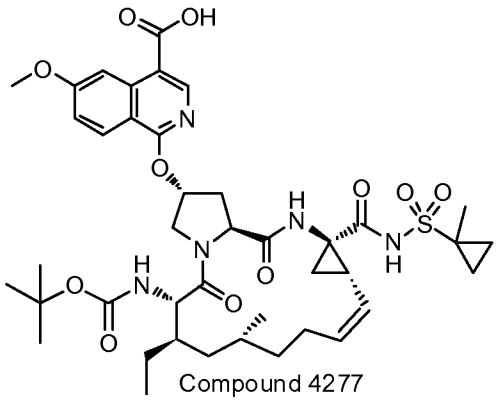
Preparation of Compound 4276



Compound 4276

Compound 4276 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3 Compound 4276: 1-(((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-6-((((1,1,1-trifluoro-2-methylpropan-2-yl)oxy)carbonyl)amino)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-2-yl)oxy)-6-methoxyisoquinoline-4-carboxylic acid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.07 (s, 1 H) 8.85 (s, 1 H) 8.51 (s, 1 H) 8.20 (s, 1 H) 7.92 (s, 1 H) 7.19 (d, *J*=9.29 Hz, 1 H) 5.99 (br. s., 1 H) 5.63 (d, *J*=6.78 Hz, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.79 - 4.83 (m, 1 H) 4.68 (br. s., 1 H) 4.05 (d, *J*=4.52 Hz, 2 H) 3.98 (s, 3 H) 2.73 - 2.81 (m, 2 H) 2.46 (d, *J*=13.05 Hz, 2 H) 1.95 - 2.02 (m, 2 H) 1.73 - 1.80 (m, 2 H) 1.67 (d, *J*=10.79 Hz, 2 H) 1.51 - 1.60 (m, 6 H) 1.28 - 1.37 (m, 5 H) 1.13 (br. s., 1 H) 1.03 (br. s., 3 H) 0.94 (m, 4H) 0.83 (m, 3 H). MS: MS *m/z* 880.2 (M^++1).

Preparation of Compound 4277

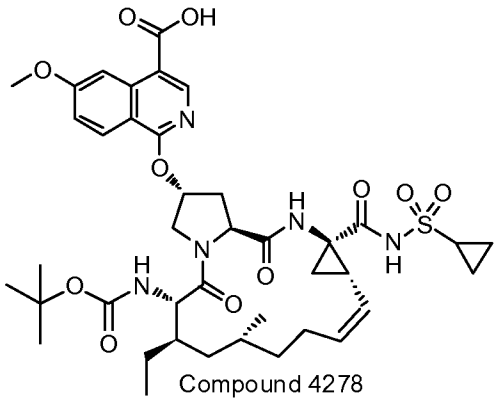


Compound 4277

Compound 4277 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001 Compound 4277: 1-(((2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-((tert-butoxycarbonyl)amino)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-2-yl)oxy)-6-methoxyisoquinoline-4-carboxylic acid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.81 (s, 1 H) 8.48 (s, 1 H) 8.18 (s, 1 H) 7.09 - 7.19 (m, 1 H) 5.93 - 6.00 (m, 1 H) 5.55 - 5.66 (m, 1 H) 4.99 (t, *J*=10.04 Hz, 1 H) 4.80

(br. s., 1 H) 4.62 (dd, *J*=10.16, 7.15 Hz, 1 H) 4.00 - 4.09 (m, 2 H) 3.95 (s, 3 H) 2.64 - 2.79 (m, 2 H) 2.43 (d, *J*=10.04 Hz, 2 H) 1.95 (d, *J*=13.30 Hz, 2 H) 1.75 (dd, *J*=8.28, 5.52 Hz, 1 H) 1.37 - 1.67 (m, 12 H) 1.03 - 1.18 (m, 10 H) 0.99 (d, *J*=6.53 Hz, 5 H) 0.78 - 0.89 (m, 3 H). MS: MS *m/z* 826.4 (M^++1).

Preparation of Compound 4278

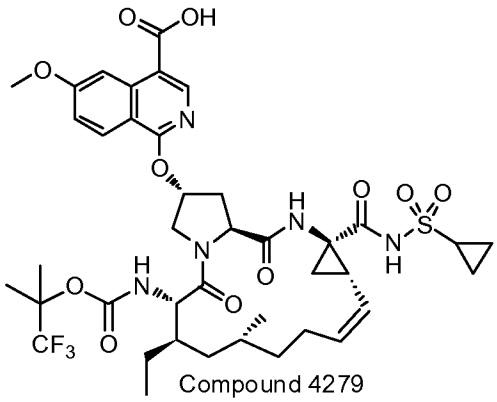


Compound 4278

Compound 4278 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4278: 1-(((2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-((tert-butoxycarbonyl)amino)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-2-yl)oxy)-6-methoxyisoquinoline-4-carboxylic acid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.81 (s, 1 H) 8.47 (d, *J*=2.51 Hz, 1 H) 8.17 (d, *J*=9.03 Hz, 1 H) 7.13 (dd, *J*=9.16, 2.38 Hz, 1 H) 5.96 (br. s., 1 H) 5.53 - 5.66 (m, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.99 (t, *J*=10.04 Hz, 1 H) 4.80 (br. s., 1 H) 4.61 (dd, *J*=10.04, 7.03 Hz, 1 H) 3.98 - 4.10 (m, 2 H) 3.96 (s, 3 H) 2.86 - 2.97 (m, 1 H) 2.63 - 2.78 (m, 2 H) 2.34 - 2.48 (m, 2 H) 1.87 - 2.02 (m, 2 H) 1.76 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.38 - 1.65 (m, 6 H) 1.15 - 1.35 (m, 2 H) 0.94 - 1.15 (m, 15H) 0.82 (t, *J*=7.40 Hz, 3 H). MS: MS *m/z* 812.2 (M^++1).

Preparation of Compound 4279

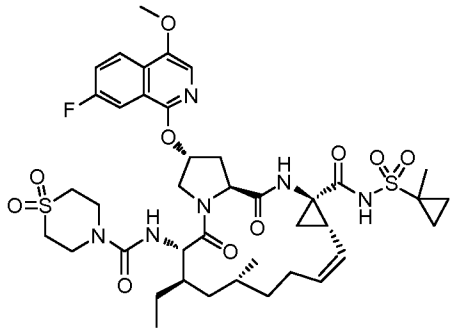


Compound 4279

Compound 4279 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

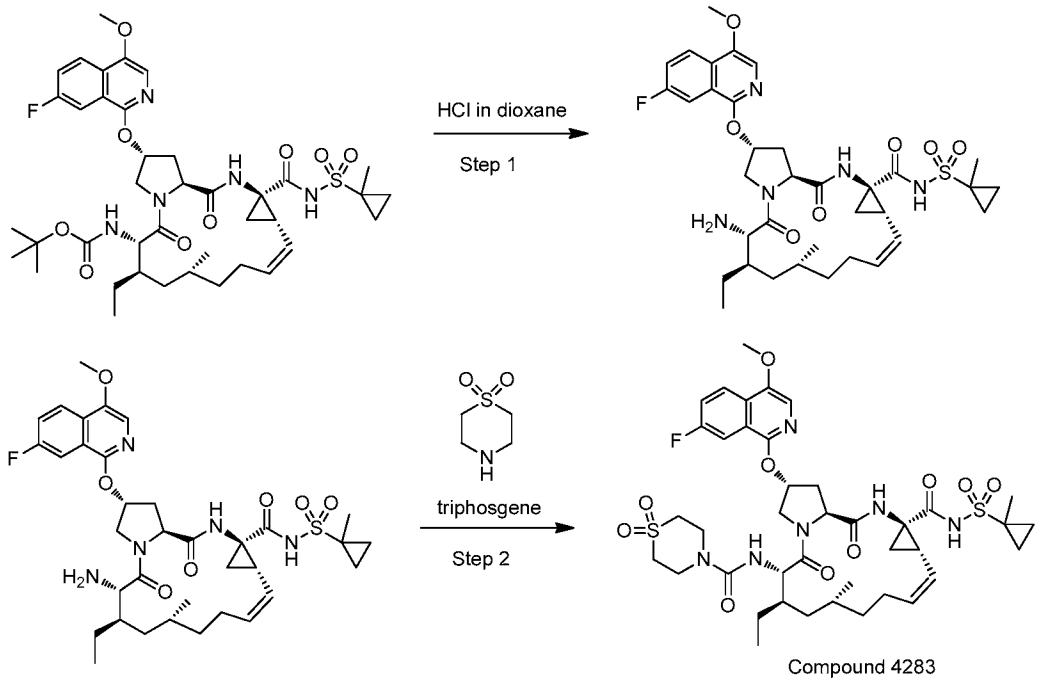
Compound 4279: 1-(((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-5,16-dioxo-6-((((1,1,1-trifluoro-2-methylpropan-2-yl)oxy)carbonyl)amino)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-2-yl)oxy)-6-methoxyisoquinoline-4-carboxylic acid. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.07 (s, 1 H) 8.85 (s, 1 H) 8.51 (s, 1 H) 8.20 (s, 1 H) 7.92 (s, 1 H) 7.19 (d, *J*=9.29 Hz, 1 H) 5.99 (br. s., 1 H) 5.63 (d, *J*=6.78 Hz, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.79 - 4.83 (m, 1 H) 4.68 (br. s., 1 H) 4.05 (d, *J*=4.52 Hz, 2 H) 3.98 (s, 3 H) 2.73 - 2.81 (m, 2 H) 2.46 (d, *J*=13.05 Hz, 2 H) 1.95 - 2.02 (m, 2 H) 1.73 - 1.80 (m, 2 H) 1.67 (d, *J*=10.79 Hz, 2 H) 1.51 - 1.60 (m, 6 H) 1.28 - 1.37 (m, 5 H) 1.13 (br. s., 1 H) 1.03 (br. s., 3 H) 0.94 (m, 4H) 0.83 (m, 3 H). MS: MS *m/z* 866.2 (M^++1).

Preparation of Compound 4283



Compound 4283

Scheme:



The intermediate tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate was prepared by following the general procedure described for the synthesis of 3117 and using the intermediates described herein.

Step 1:

To a solution of HCl in 1,4-dioxane (4.0 M, 125 mL) was added tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate (4.8 g, 6.00 mmol). The solution was stirred at room temperature for 1h. The volatiles were removed under reduced pressure. The resulting residue was washed with diethyl ether to afford (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-7-ethyl-2-((7-fluoro-4-

methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide HCl salt (3.85 g, 4.18 mmol, 69.7 % yield) as solid. MS: MS *m/z* 700.56 (M^++1). The compound was carried into step 2 without further purification.

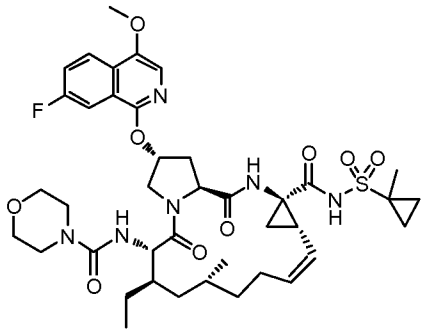
Step 2:

To a stirred solution of (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-amino-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide HCl salt (0.05 g, 0.068 mmol) in THF (2.5 mL) at 0 °C was added *N,N*-diisopropylethylamine (0.059 mL, 0.340 mmol) followed by the addition of triphosgene (6.05 mg, 0.020 mmol). The reaction mixture was stirred for 2h at room temperature. To the solution was added thiomorpholine 1,1-dioxide (9.18 mg, 0.068 mmol), then the solution stirred overnight. The reaction mixture was diluted with methylenechloride (50 mL) and washed with water. The organic layer was dried over anhydrous sodium sulfate; filtered; then concentrated under reduced pressure. The resulting residue was purified by HPLC to afford Compound 4283 as a solid (0.025 g, 42 % yield).

Compound 4283: N-((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)thiomorpholine-4-carboxamide 1,1-dioxide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.00 (s, 1 H) 8.18 (dd, *J*=9.16, 5.40 Hz, 1 H) 7.83 (dd, *J*=9.79, 2.51 Hz, 1 H) 7.50 - 7.59 (m, 2 H) 5.86 (br. s., 1 H) 5.64 (d, *J*=6.02 Hz, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.77 - 4.82 (m, 1 H) 4.60 (dd, *J*=9.91, 7.15 Hz, 1 H) 4.30 (d, *J*=11.29 Hz, 1 H) 4.00 (d, *J*=3.51 Hz, 4 H) 3.47 - 3.56 (m, 4 H) 3.12 - 3.22 (m, 4 H) 2.70 - 2.79 (m, 3 H) 2.39 - 2.51 (m, 2 H) 1.95 - 2.09 (m, 3 H) 1.78 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.62 - 1.69 (m, 4 H) 1.56 (d, *J*=4.02 Hz, 7 H) 1.41 - 1.48 (m, 3 H) 1.28

- 1.35 (m, 2 H) 1.17 (t, *J*=12.17 Hz, 1 H) 1.03 (d, *J*=6.78 Hz, 3 H) 0.81 - 0.95 (m, 6 H). MS: MS *m/z* 837.8 (M^++1).

Preparation of Compound 4284

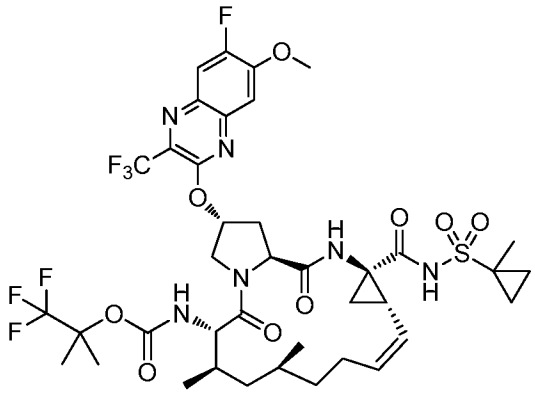


Compound 4284

Compound 4284 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4283.

Compound 4284: N-((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)morpholine-4-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.00 (s, 1 H) 8.18 (dd, *J*=9.16, 5.40 Hz, 1 H) 7.83 (dd, *J*=9.79, 2.51 Hz, 1 H) 7.50 - 7.59 (m, 2 H) 5.86 (br. s., 1 H) 5.64 (d, *J*=6.02 Hz, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.77 - 4.82 (m, 1 H) 4.60 (dd, *J*=9.91, 7.15 Hz, 1 H) 4.30 (d, *J*=11.29 Hz, 1 H) 4.00 (d, *J*=3.51 Hz, 4 H) 3.47 - 3.56 (m, 4 H) 3.12 - 3.22 (m, 4 H) 2.70 - 2.79 (m, 3 H) 2.39 - 2.51 (m, 2 H) 1.95 - 2.09 (m, 3 H) 1.78 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.62 - 1.69 (m, 4 H) 1.56 (d, *J*=4.02 Hz, 7 H) 1.41 - 1.48 (m, 3 H) 1.28 - 1.35 (m, 2 H) 1.17 (t, *J*=12.17 Hz, 1 H) 1.03 (d, *J*=6.78 Hz, 3 H) 0.81 - 0.95 (m, 6 H). MS: MS *m/z* 813.6 (M^++1).

Preparation of Compound 4289

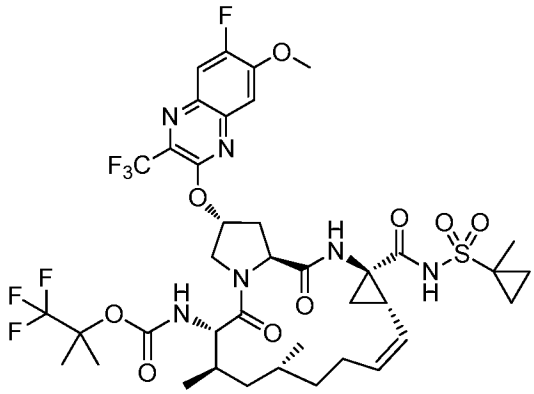


Compound 4289

Compound 4289 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4289: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.91 (s, 1 H) 7.78 (d, *J*=11.04 Hz, 2 H) 7.55 (d, *J*=8.28 Hz, 2 H) 5.97 (br. s., 2 H) 5.68 (d, *J*=8.53 Hz, 1 H) 4.71 (dd, *J*=9.29, 7.53 Hz, 1 H) 4.60 (d, *J*=11.80 Hz, 1 H) 4.12 (m, 4 H) 4.02 (d, *J*=7.03 Hz, 1 H) 2.69 (m, 1 H) 2.52 (m, 3 H) 1.97 (m, 3 H) 1.72 (m, 1 H) 1.62 (dd, *J*=9.54, 5.27 Hz, 3 H) 1.52 (s, 3 H) 1.42 (m, 3 H) 1.30 (m, 8 H) 1.20 (m, 1 H) 1.07 (d, *J*=6.78 Hz, 3 H) 0.92 (d, *J*=7.03 Hz, 3 H) 0.84 (br. s., 2 H). ^{19}F NMR: δ ppm -69.63 (3F) -85.88 (3F) -132.29 (1F). MS: MS *m/z* 907.2 (M^{+}-1).

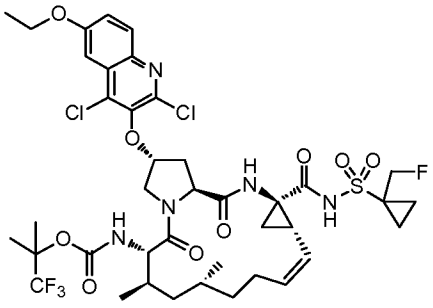
Preparation of Compound 4290



Compound 4290

Compound 4290 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4290: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm .91 (s, 1 H) 7.79 (d, *J*=11.29 Hz, 1 H) 7.55 (d, *J*=8.28 Hz, 1 H) 5.96 (br. s., 1 H) 5.61 (d, *J*=5.77 Hz, 1 H) 4.79 (s, 1 H) 4.62 (m, 1 H) 4.12 (s, 3 H) 4.05 (dd, *J*=11.92, 2.89 Hz, 1 H) 3.73 (d, *J*=10.79 Hz, 1 H) 3.50 (m, 1 H) 3.15 (m, 1 H) 2.72 (m, 2 H) 2.48 (m, 2 H) 1.83 (m, 5 H) 1.59 (m, 2 H) 1.46 (m, 7 H) 1.31 (s, 1 H) 1.24 (m, 7 H) 1.01 (d, *J*=6.78 Hz, 3 H) 0.96 (d, *J*=6.53 Hz, 3 H) 0.83 (m, 3 H). ^{19}F NMR: δ ppm -69.63 (3F) -85.94 (3F) -132.29 (1F). MS: MS *m/z* 907.2 (M^{+}+1).

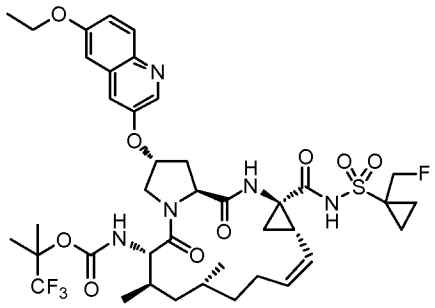
Preparation of Compound 4292



Compound 4292

Compound 4292 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3 Compound 4292: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,4-dichloro-6-ethoxyquinolin-3-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.17 (s, 1 H) 7.83 - 7.90 (m, 1 H) 7.40 - 7.49 (m, 2 H) 5.53 - 5.64 (m, 2 H) 5.01 (t, *J*=10.04 Hz, 1 H) 4.69 - 4.80 (m, 1 H) 4.60 (d, *J*=11.04 Hz, 1 H) 4.50 (s, 1 H) 4.38 (d, *J*=12.05 Hz, 1 H) 4.25 (q, *J*=7.03 Hz, 2 H) 3.89 - 4.03 (m, 2 H) 2.64 - 2.81 (m, 2 H) 2.34 - 2.48 (m, 2 H) 1.92 - 2.04 (m, 2 H) 1.82 (dd, *J*=13.30, 6.27 Hz, 1 H) 1.60 - 1.76 (m, 10 H) 1.42 - 1.57 (m, 5 H) 1.11 - 1.32 (m, 4 H) 0.99 (dd, *J*=8.78, 6.78 Hz, 6 H) 0.81 (t, *J*=11.55 Hz, 1 H). MS: MS *m/z* 923.7(M^++1).

Preparation of Compound 4296

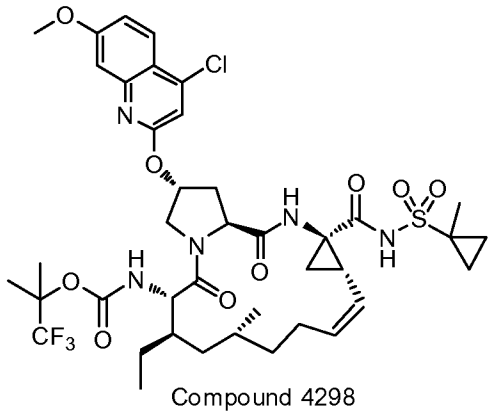


Compound 4296

Compound 4296 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3 Compound 4296: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyquinolin-3-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.10 (s, 1 H) 8.52 (s, 1 H) 7.98 (br. s., 1 H) 7.90 (d, *J*=9.54 Hz, 1 H) 7.33 - 7.41 (m, 1 H) 5.63 (td, *J*=10.16, 5.77 Hz, 1 H) 5.44 (br. s., 1 H) 5.01 (t, *J*=10.04 Hz, 1 H) 4.79

(d, *J*=11.04 Hz, 1 H) 4.44 - 4.72 (m, 2 H) 4.24 (q, *J*=7.03 Hz, 1 H) 4.05 (dd, *J*=11.55, 3.51 Hz, 1 H) 3.80 - 3.91 (m, 1 H) 3.48 - 3.55 (m, 1 H) 3.16 (quin, *J*=1.76 Hz, 1 H) 2.62 - 2.76 (m, 4 H) 2.37 - 2.56 (m, 4 H) 1.63 - 1.83 (m, 5 H) 1.56 - 1.62 (m, 2 H) 1.43 - 1.55 (m, 10 H) 1.30 - 1.36 (m, 6 H) 1.14 - 1.29 (m, 1 H) 0.94 - 1.07 (m, 1 H) 0.67 - 0.88 (m, 2 H). MS: MS *m/z* 854.8 (M^++1).

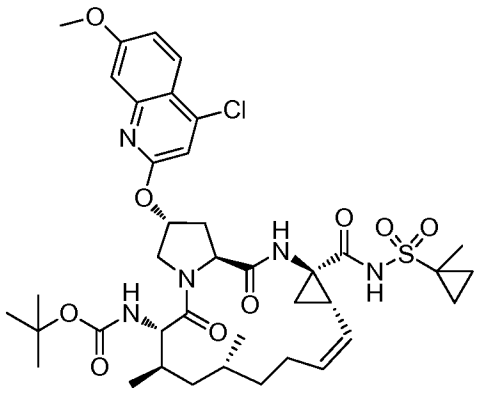
Preparation of Compound 4298



Compound 4298

Compound 4298 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3 Compound 4298: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-chloro-7-methoxyquinolin-2-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.02 (d, *J*=9.04 Hz, 1 H) 7.34 (d, *J*=2.51 Hz, 1 H) 7.18 (dd, *J*=9.04, 2.51 Hz, 1 H) 6.92 (s, 1 H) 5.93 (br. s., 1 H) 4.69 (d, *J*=12.05 Hz, 1 H) 4.59 (br. s., 1 H) 4.07 (d, *J*=11.04 Hz, 2 H) 3.98 (s, 3 H) 2.63 (d, *J*=6.02 Hz, 1 H) 2.42 - 2.48 (m, 1 H) 1.92 - 2.03 (m, 2 H) 1.74 - 1.81 (m, 1 H) 1.52 - 1.62 (m, 6 H) 1.42 (br. s., 2 H) 1.31 (s, 8 H) 1.08 - 1.17 (m, 8 H) 0.78 - 1.03 (m, 10 H). MS: MS *m/z* 867.9 (M^++1).

Preparation of Compound 4300

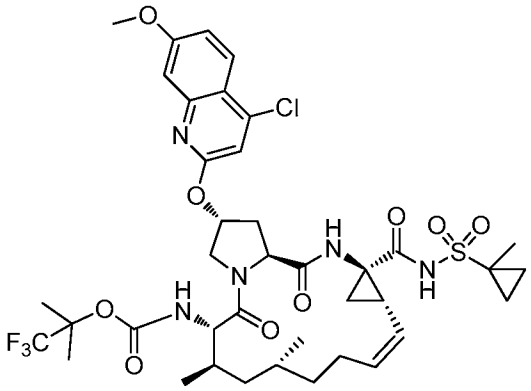


Compound 4300

Compound 4300 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4300: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-chloro-7-methoxyquinolin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.01 (d, *J*=9.04 Hz, 1 H) 7.33 (d, *J*=2.51 Hz, 1 H) 7.17 (dd, *J*=9.04, 2.51 Hz, 1 H) 6.90 (s, 1 H) 5.93 (br. s., 1 H) 5.63 (d, *J*=6.02 Hz, 1 H) 5.02 (br. s., 1 H) 4.48 - 4.70 (m, 2 H) 4.05 - 4.15 (m, 1 H) 3.98 (s, 3 H) 3.87 (d, *J*=10.54 Hz, 1 H) 3.45 - 3.56 (m, 1 H) 3.13 - 3.24 (m, 1 H) 2.60 - 2.82 (m, 2 H) 2.39 - 2.54 (m, 2 H) 1.97 - 2.04 (m, 1 H) 1.76 - 1.92 (m, 2 H) 1.58 - 1.64 (m, 1 H) 1.53 (s, 4 H) 1.30 - 1.34 (m, 1 H) 1.18 (s, 9 H) 1.06 - 1.12 (m, 1 H) 1.02 (d, *J*=7.03 Hz, 4 H) 0.97 (d, *J*=6.02 Hz, 4 H) 0.90 (br. s., 2 H) 0.74 - 0.84 (m, 2 H). MS: MS *m/z* 799.9 (M^+-1).

Preparation of Compound 4302

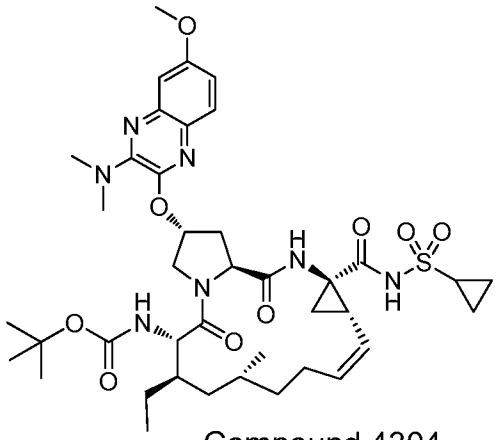


Compound 4302

Compound 4302 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4302: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-chloro-7-methoxyquinolin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.02 (d, *J*=9.04 Hz, 1 H) 7.34 (d, *J*=2.51 Hz, 1 H) 7.18 (dd, *J*=9.04, 2.51 Hz, 1 H) 6.92 (s, 1 H) 5.91 (br. s., 1 H) 5.52 - 5.71 (m, 1 H) 5.02 (t, *J*=9.79 Hz, 1 H) 4.51 - 4.75 (m, 2 H) 4.06 (dd, *J*=11.55, 4.02 Hz, 1 H) 3.98 (s, 3 H) 3.84 (d, *J*=11.04 Hz, 1 H) 2.56 - 2.84 (m, 2 H) 2.45 (dd, *J*=13.80, 9.79, 4.52 Hz, 2 H) 1.85 - 2.13 (m, 2 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 2 H) 1.57 - 1.71 (m, 2 H) 1.53 - 1.57 (m, 3 H) 1.38 - 1.50 (m, 3 H) 1.34 (s, 3 H) 1.22 - 1.32 (m, 4 H) 0.94 - 1.11 (m, 6 H) 0.77 - 0.94 (m, 6 H). MS: MS *m/z* 855.8(M^++1).

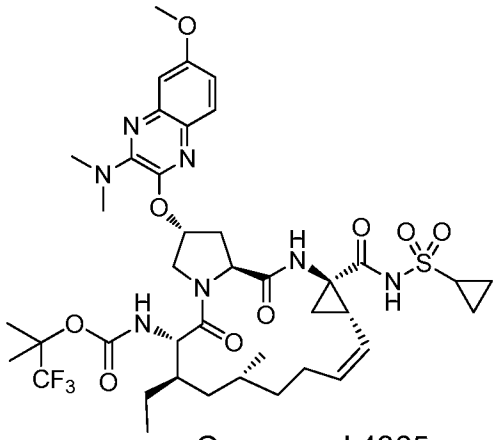
Preparation of Compound 4304



Compound 4304

Compound 4304 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001. Compound 4304: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(dimethylamino)-6-methoxyquinoxalin-2-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.60 (d, *J*=9.04 Hz, 1 H) 7.15 (d, *J*=2.51 Hz, 1 H) 7.04 (dd, *J*=8.78, 2.76 Hz, 1 H) 5.97 (br. s., 1 H) 5.64 (td, *J*=10.04, 6.02 Hz, 1 H) 4.93 - 5.14 (m, 1 H) 4.73 (d, *J*=12.05 Hz, 1 H) 4.58 (dd, *J*=9.79, 7.28 Hz, 1 H) 4.01 - 4.14 (m, 1 H) 3.90 (s, 3 H) 3.21 - 3.29 (m, 6 H) 2.86 - 3.01 (m, 1 H) 2.64 - 2.78 (m, 2 H) 2.33 - 2.52 (m, 2 H) 1.88 - 2.06 (m, 2 H) 1.79 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.47 - 1.72 (m, 6 H) 1.21 - 1.43 (m, 11 H) 0.98 - 1.22 (m, 9 H) 0.75 - 0.97 (m, 3 H). MS: MS *m/z* 812.55 (M^++1).

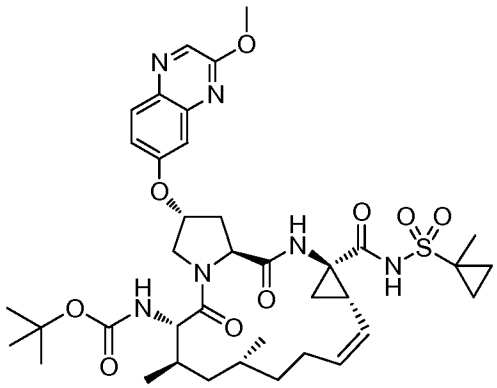
Preparation of Compound 4305



Compound 4305

Compound 4305 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4305: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(dimethylamino)-6-methoxyquinoxalin-2-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.62 (d, *J*=9.04 Hz, 1 H) 7.16 (d, *J*=2.51 Hz, 1 H) 7.06 (dd, *J*=9.04, 3.01 Hz, 1 H) 5.86 - 6.02 (m, 1 H) 5.64 (td, *J*=10.29, 6.02 Hz, 1 H) 5.05 (t, *J*=9.79 Hz, 1 H) 4.73 (d, *J*=11.04 Hz, 1 H) 4.59 (dd, *J*=10.04, 7.03 Hz, 1 H) 3.98 - 4.13 (m, 2 H) 3.91 (s, 3 H) 3.20 - 3.30 (m, 6 H) 2.85 - 3.01 (m, 1 H) 2.70 (q, *J*=9.20 Hz, 2 H) 2.31 - 2.55 (m, 2 H) 1.89 - 2.08 (m, 2 H) 1.79 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.45 - 1.67 (m, 6 H) 1.26 - 1.46 (m, 9 H) 0.97 - 1.27 (m, 9 H) 0.83 (t, *J*=7.53 Hz, 3 H). ^{19}F NMR: δ ppm -84.89 (3F). MS: MS *m/z* 865.96 (M^{+}+1).

Preparation of Compound 4310

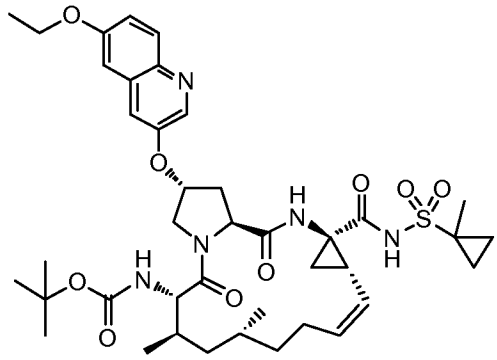


Compound 4310

Compound 4310 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001.

Compound 4310: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-methoxyquinoxalin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.32 (s, 1 H) 7.88 (d, *J*=9.54 Hz, 1 H) 7.26 (m, 2 H) 5.62 (td, *J*=9.91, 5.77 Hz, 1 H) 5.40 (br. s., 1 H) 5.01 (t, *J*=9.79 Hz, 1 H) 4.57 (m, 2 H) 4.10 (m, 4 H) 3.90 (d, *J*=11.04 Hz, 1 H) 2.71 (m, 2 H) 2.44 (m, 2 H) 1.95 (m, 2 H) 1.72 (m, 3 H) 1.49 (m, 7 H) 1.25 (m, 11 H) 0.92 (m, 9 H). MS: MS *m/z* 766.8 (M^+-1).

Preparation of Compound 4311

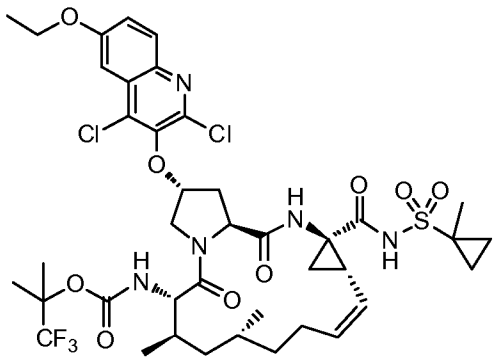


Compound 4311

Compound 4311 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001.

Compound 4311: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyquinolin-3-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.81 (s, 1 H) 8.44 (s, 1 H) 8.21 (s, 1 H) 7.19 - 7.22 (m, 1 H) 5.99 (br. s., 1 H) 5.63 (d, *J*=6.02 Hz, 1 H) 5.02 (s, 1 H) 4.81 (s, 1 H) 4.66 - 4.71 (m, 1 H) 4.02 - 4.07 (m, 2 H) 3.99 (s, 6 H) 2.72 - 2.80 (m, 2 H) 2.46 (d, *J*=13.80 Hz, 2 H) 1.99 (br. s., 2 H) 1.78 (d, *J*=3.01 Hz, 1 H) 1.64 - 1.69 (m, 1 H) 1.55 - 1.62 (m, 6 H) 1.44 (dd, *J*=9.66, 4.64 Hz, 2 H) 1.24 - 1.35 (m, 6 H) 1.13 (s, 2 H) 1.02 (d, *J*=6.78 Hz, 3 H) 0.94 (s, 4 H) 0.83 (t, *J*=7.40 Hz, 3 H). MS: MS *m/z* 782.4 (M^++1).

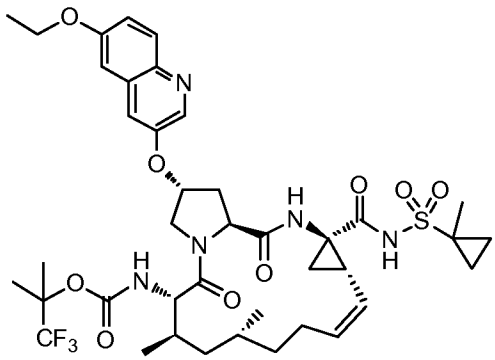
Preparation of Compound 4312



Compound 4312

Compound 4312 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3 Compound 4312: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,4-dichloro-6-ethoxyquinolin-3-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.84 - 7.88 (m, 1 H) 7.39 - 7.49 (m, 2 H) 5.60 (d, *J*=5.52 Hz, 2 H) 4.75 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.38 (d, *J*=11.04 Hz, 1 H) 4.24 (q, *J*=7.03 Hz, 2 H) 3.91 - 4.04 (m, 2 H) 3.01 - 3.08 (m, 1 H) 2.77 (dd, *J*=14.06, 6.53 Hz, 2 H) 2.34 - 2.52 (m, 2 H) 1.87 - 2.06 (m, 2 H) 1.73 - 1.86 (m, 2 H) 1.56 - 1.68 (m, 7 H) 1.39 - 1.54 (m, 9 H) 1.20 - 1.34 (m, 3 H) 0.94 - 1.02 (m, 6 H) 0.77 - 0.88 (m, 3 H). MS: MS *m/z* 904.4 (M^++1).

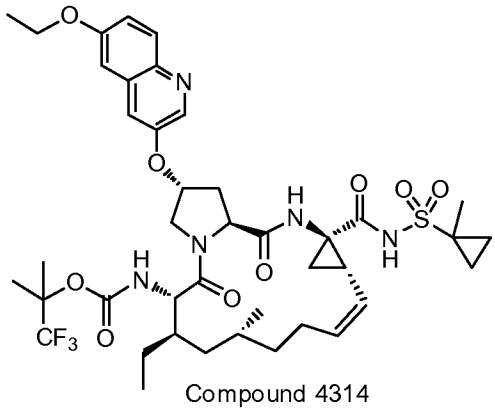
Preparation of Compound 4313



Compound 4313

Compound 4313 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3 Compound 4313: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyquinolin-3-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.36 (d, *J*=3.01 Hz, 1 H) 7.84 (d, *J*=8.53 Hz, 1 H) 7.72 (d, *J*=2.51 Hz, 1 H) 7.39 (d, *J*=9.04 Hz, 1 H) 7.23 - 7.31 (m, 2 H) 5.64 (td, *J*=10.29, 6.02 Hz, 1 H) 5.39 (br. s., 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.71 (d, *J*=10.04 Hz, 1 H) 4.60 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.22 (q, *J*=7.03 Hz, 2 H) 4.01 - 4.11 (m, 2 H) 2.64 - 2.74 (m, 2 H) 2.45 (ddd, *J*=13.93, 9.91, 4.77 Hz, 2 H) 1.91 - 2.07 (m, 2 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.62 - 1.69 (m, 1 H) 1.58 (dd, *J*=9.54, 5.52 Hz, 3 H) 1.48 - 1.54 (m, 7 H) 1.44 (dd, *J*=8.78, 5.27 Hz, 1 H) 1.34 (s, 3 H) 1.19 - 1.29 (m, 2H) 1.09 - 1.16 (m, 3 H) 1.01 (d, *J*=6.53 Hz, 3 H) 0.87 - 0.93 (m, 4 H) 0.82 (t, *J*=7.53 Hz, 3 H). MS: MS *m/z* 836.3 (M^++1).

Preparation of Compound 4314

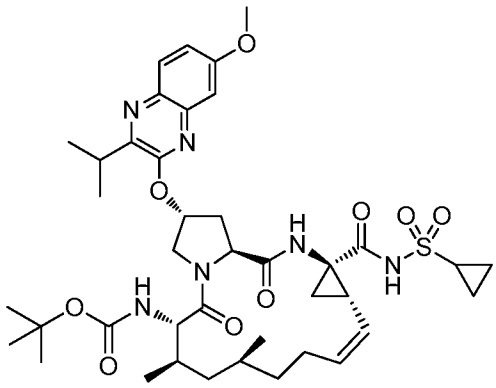


Compound 4314

Compound 4314 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3

Compound 4314: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyquinolin-3-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.36 (d, *J*=3.01 Hz, 1 H) 7.84 (d, *J*=8.53 Hz, 1 H) 7.72 (d, *J*=2.51 Hz, 1 H) 7.39 (d, *J*=9.04 Hz, 1 H) 7.23 - 7.31 (m, 2 H) 5.64 (td, *J*=10.29, 6.02 Hz, 1 H) 5.39 (br. s., 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.71 (d, *J*=10.04 Hz, 1 H) 4.60 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.22 (q, *J*=7.03 Hz, 2 H) 4.01 - 4.11 (m, 2 H) 2.64 - 2.74 (m, 2 H) 2.45 (ddd, *J*=13.93, 9.91, 4.77 Hz, 2 H) 1.91 - 2.07 (m, 2 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.62 - 1.69 (m, 1 H) 1.58 (dd, *J*=9.54, 5.52 Hz, 3 H) 1.48 - 1.54 (m, 7 H) 1.44 (dd, *J*=8.78, 5.27 Hz, 1 H) 1.34 (s, 3 H) 1.19 - 1.29 (m, 2H) 1.09 - 1.16 (m, 2 H) 1.01 (d, *J*=6.53 Hz, 3 H) 0.87 - 0.93 (m, 4 H) 0.82 (t, *J*=7.53 Hz, 3 H). MS: MS *m/z* 850.4 (M^++1).

Preparation of Compound 4315

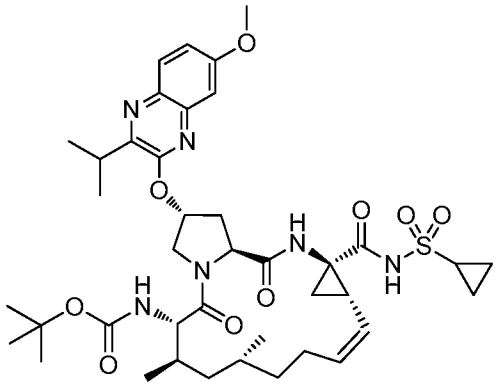


Compound 4315

Compound 4315 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001.

Compound 4315: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.92 (s, 1 H) 7.83 (d, *J*=9.04 Hz, 1 H) 7.24 (m, 2 H) 5.97 (br. s., 1 H) 5.72 (d, *J*=9.04 Hz, 1 H) 4.68 (t, *J*=8.28 Hz, 1 H) 4.43 (d, *J*=12.05 Hz, 1 H) 4.16 (d, *J*=6.53 Hz, 2 H) 3.96 (s, 3 H) 3.48 (m, 1 H) 2.91 (br. s., 1 H) 2.61 (m, 2 H) 2.02 (m, 3 H) 1.74 (m, 2 H) 1.35 (m, 10 H) 1.13 (m, 13 H) 0.95 (m, 4 H). MS: MS *m/z* 797.2 (M^++1).

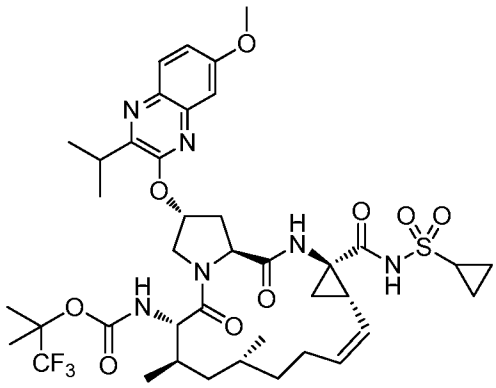
Preparation of Compound 4316



Compound 4316

Compound 4316 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001. Compound 4316: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.92 (s, 1 H) 7.83 (d, *J*=9.04 Hz, 1 H) 7.23 (m, 2 H) 5.95 (br. s., 1 H) 5.59 (m, 1 H) 4.62 (m, 2 H) 4.09 (dd, *J*=11.55, 3.51 Hz, 1 H) 3.96 (s, 3 H) 3.88 (d, *J*=11.04 Hz, 1 H) 3.47 (m, 1 H) 3.16 (t, *J*=1.51 Hz, 1 H) 2.93 (m, 1 H) 2.71 (m, 2 H) 2.46 (m, 1 H) 1.91 (m, 4 H) 1.57 (m, 3 H) 1.31 (m, 8 H) 1.12 (m, 9 H) 0.92 (m, 9 H). MS: MS *m/z* 797.4 (M^++1).

Preparation of Compound 4317

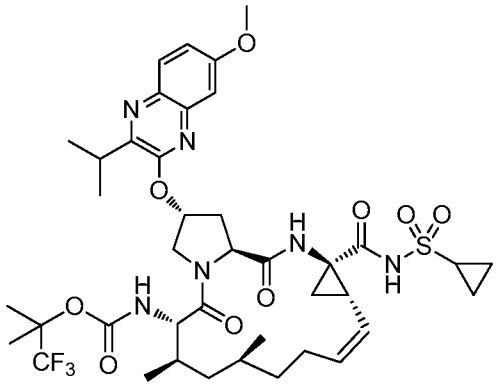


Compound 4317

Compound 4317 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4317: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.87 (m, 1 H) 7.24 (m, 2 H) 5.95 (br. s., 1 H) 5.73 (m, 1 H) 5.12 (br. s., 1 H) 4.70 (dd, *J*=9.79, 7.28 Hz, 1 H) 4.47 (d, *J*=11.55 Hz, 1 H) 4.12 (d, *J*=7.03 Hz, 2 H) 3.96 (m, 3 H) 3.47 (m, 1 H) 2.92 (br. s., 1 H) 2.71 (m, 2 H) 2.50 (m, 2 H) 2.03 (m, 2 H) 1.70 (m, 3 H) 1.46 (m, 5 H) 1.28 (m, 9 H) 1.02 (m, 9 H). ^{19}F NMR: δ ppm -85.01 (3F). MS: MS *m/z* 851.2 (M^++1).

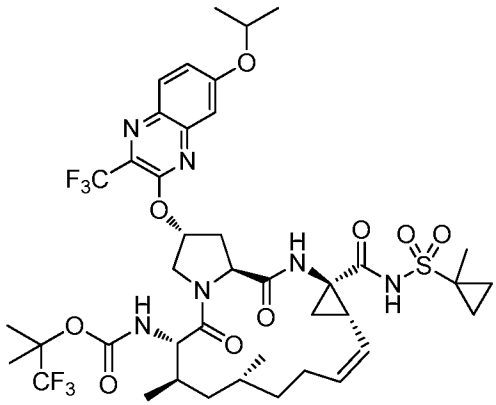
Preparation of Compound 4318



Compound 4318

Compound 4318 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4318: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.84 (d, *J*=9.04 Hz, 1 H) 7.24 (m, 2 H) 5.95 (br. s., 1 H) 5.74 (d, *J*=10.04 Hz, 1 H) 4.70 (m, 1 H) 4.51 (m, 1 H) 4.11 (d, *J*=7.03 Hz, 2 H) 3.95 (s, 3 H) 3.47 (m, 1 H) 2.93 (d, *J*=5.52 Hz, 1 H) 2.71 (m, 1 H) 2.50 (d, *J*=19.07 Hz, 1 H) 2.03 (m, 1 H) 1.68 (m, 3 H) 1.33 (m, 17 H) 1.04 (m, 8 H). ^{19}F NMR: δ ppm -85.02 (3F). MS: MS *m/z* 851.2 (M^{+}+1).

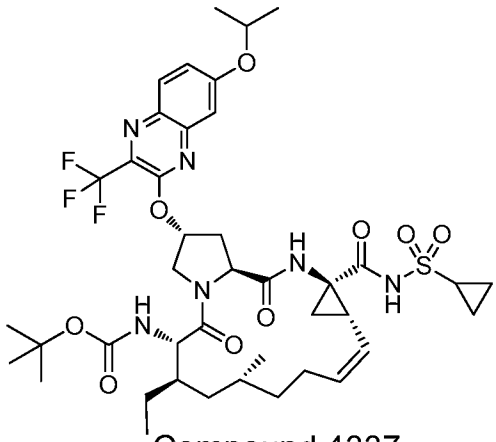
Preparation of Compound 4336



Compound 4336

Compound 4336 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4336: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-isopropoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.98 (d, *J*=9.04 Hz, 1 H) 7.28 - 7.40 (m, 2 H) 5.90 - 6.04 (m, 1 H) 5.52 - 5.71 (m, 1 H) 4.64 (dd, *J*=10.29, 7.28 Hz, 1 H)) 4.01 - 4.12 (m, 1 H) 3.71 - 3.83 (m, 1 H) 2.64 - 2.79 (m, 2 H) 2.36 - 2.56 (m, 2 H) 1.71 - 2.03 (m, 4 H) 1.55 - 1.65 (m, 2 H) 1.37 - 1.52 (m, 12 H) 1.14 - 1.28 (m, 8 H) 0.93 - 1.07 (m, 8 H) 0.74 - 0.91 (m, 6 H). ^{19}F NMR: δ ppm -68.75 (3F) -85.16 (3F). MS: MS *m/z* 919.81 (M^++1).

Preparation of Compound 4337

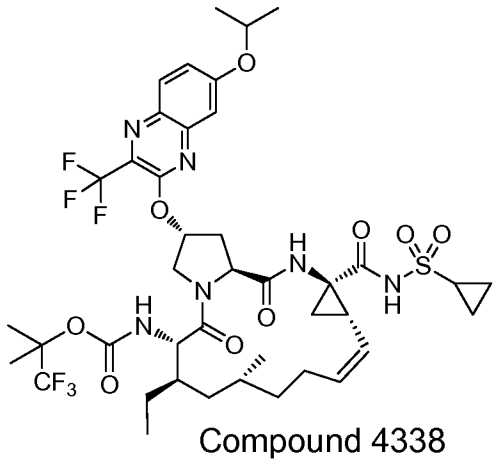


Compound 4337

Compound 4337 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001.

Compound 4337: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-isopropoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.96 (d, *J*=9.04 Hz, 1 H) 7.36 (d, *J*=5.02 Hz, 2 H) 5.96 - 6.06 (m, 1 H) 5.62 (d, *J*=7.03 Hz, 1 H) 4.57 - 4.67 (m, 1 H) 3.97 - 4.12 (m, 2 H) 2.92 (br. s., 1 H) 2.70 (d, *J*=6.02 Hz, 2 H) 2.36 - 2.55 (m, 1 H) 1.89 - 2.07 (m, 2 H) 1.78 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.39 - 1.66 (m, 12 H) 1.12 - 1.26 (m, 8 H) 0.95 - 1.18 (m, 16 H) 0.81 (t, *J*=7.53 Hz, 3 H). MS: MS *m/z* 809.2 (M^++1).

Preparation of Compound 4338

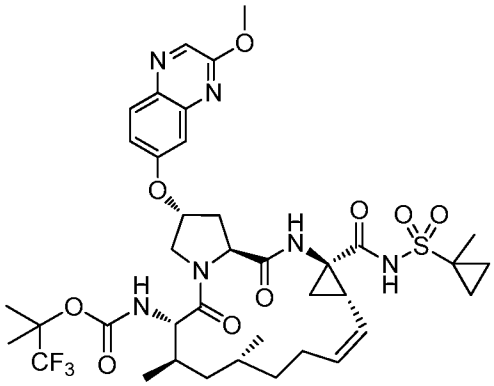


Compound 4338

Compound 4338 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4338: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-isopropoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.98 (d, *J*=9.04 Hz, 1 H) 7.30 - 7.39 (m, 2 H) 5.95 - 6.03 (m, 1 H) 5.57 - 5.67 (m, 1 H) 5.00 - 5.14 (m, 1 H) 4.80 (d, *J*=12.55 Hz, 1 H) 4.63 (dd, *J*=9.79, 7.28 Hz, 1 H) 3.94 - 4.10 (m, 2 H) 2.93 (br. s., 1 H) 2.72 (dt, *J*=13.80, 7.15 Hz, 2 H) 2.35 - 2.54 (m, 2 H) 1.98 (br. s., 2 H) 1.78 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.40 - 1.65 (m, 13 H) 1.17 - 1.36 (m, 10 H) 0.99 - 1.13 (m, 8 H) 0.74 - 0.84 (m, 3 H). ^{19}F NMR: δ ppm -68.66 (3F) -85.14 (3F). MS: MS *m/z* 919.4 (M^{+}+1).

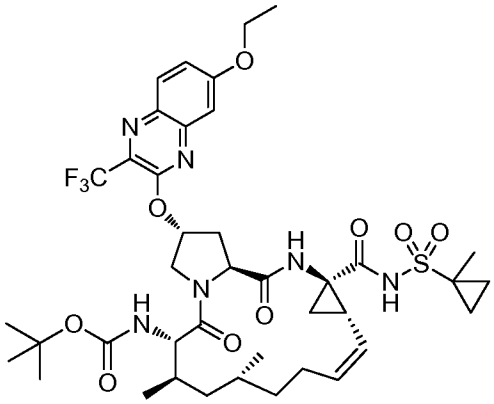
Preparation of Compound 4339



Compound 4339

Compound 4339 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4339: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-methoxyquinoxalin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.33 (s, 1 H) 7.91 (m, 1 H) 7.35 (s, 1 H) 7.25 (dd, *J*=9.04, 3.01 Hz, 1 H) 5.63 (m, 1 H) 5.42 (m, 1 H) 5.02 (br. s., 1 H) 4.60 (m, 2 H) 4.12 (s, 3 H) 4.05 (dd, *J*=11.55, 3.51 Hz, 1 H) 3.88 (d, *J*=10.54 Hz, 1 H) 3.37 (s, 4 H) 2.70 (m, 2 H) 2.43 (m, 2 H) 1.98 (m, 2 H) 1.78 (m, 2 H) 1.66 (d, *J*=9.54 Hz, 1 H) 1.57 (m, 4 H) 1.44 (m, 5 H) 1.26 (m, 4 H) 1.11 (s, 1 H) 0.98 (m, 8 H) 0.86 (m, 3 H). ^{19}F NMR: δ ppm -85.03 (3F). MS: MS *m/z* 823.2 (M^{+}+1).

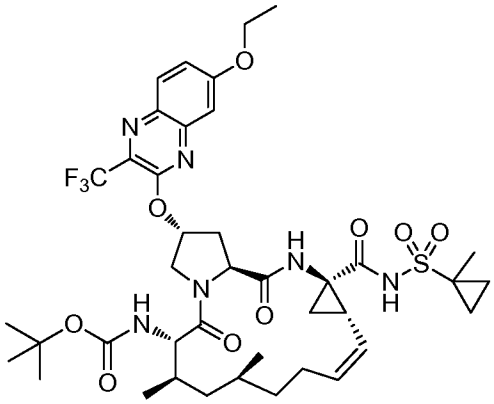
Preparation of Compound 4346



Compound 4346

Compound 4346 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001. Compound 4346: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.97 (m, 1 H) 7.37 (m, 2 H) 5.98 (br. s., 1 H) 5.62 (br. s., 1 H) 4.93 (m, 1 H) 4.80 (d, *J*=11.55 Hz, 1 H) 4.62 (m, 1 H) 4.28 (m, 2 H) 4.08 (dd, *J*=11.55, 3.51 Hz, 1 H) 3.79 (d, *J*=11.04 Hz, 1 H) 2.70 (m, 2 H) 2.49 (m, 2 H) 1.99 (br. s., 1 H) 1.79 (m, 3 H) 1.60 (m, 1 H) 1.28 (m, 10 H) 1.09 (s, 8 H) 0.97 (m, 6 H) 0.82 (m, 2 H). ^{19}F NMR: δ ppm -68.67 (3F). MS: MS *m/z* 849.1 (M^{+}-1).

Preparation of Compound 4347

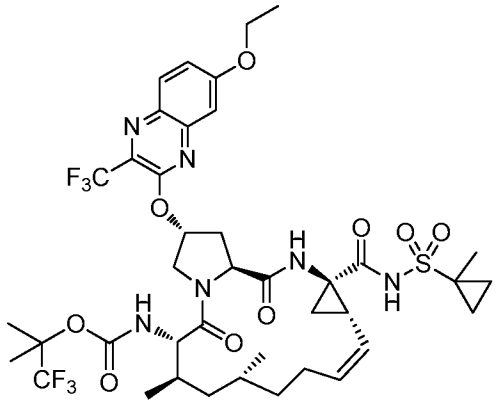


Compound 4347

Compound 4347 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001.

Compound 4347: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.97 (m, 1 H) 7.37 (dd, *J*=4.52, 2.51 Hz, 2 H) 6.00 (br. s., 1 H) 5.70 (br. s., 1 H) 4.96 (s, 1 H) 4.70 (t, *J*=8.53 Hz, 1 H) 4.56 (m, 1 H) 4.24 (m, 3 H) 4.08 (d, *J*=7.53 Hz, 1 H) 3.43 (s, 1 H) 2.63 (m, 2 H) 2.02 (m, 3 H) 1.72 (m, 4 H) 1.52 (m, 7 H) 1.41 (d, *J*=8.03 Hz, 2 H) 1.25 (d, *J*=13.05 Hz, 3 H) 1.07 (d, *J*=6.53 Hz, 11 H) 0.96 (m, 3 H) 0.83 (br. s., 2 H). ^{19}F NMR: δ ppm -68.67 (3F). MS: MS *m/z* 849.1 (M^+-1).

Preparation of Compound 4348

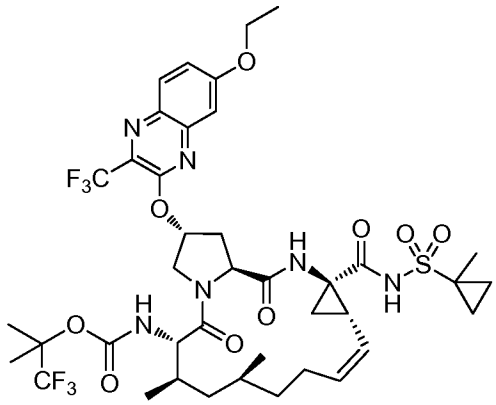


Compound 4348

Compound 4348 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4348: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.98 (m, 1 H) 7.92 (s, 1 H) 7.38 (m, 2 H) 5.97 (br. s., 1 H) 5.61 (br. s., 1 H) 5.51 (s, 1 H) 4.99 (m, 1 H) 4.81 (s, 1 H) 4.63 (m, 1 H) 4.29 (qd, *J*=7.03, 2.01 Hz, 2 H) 4.07 (m, 1 H) 3.75 (d, *J*=11.04 Hz, 1 H) 3.36 (m, 1 H) 2.73 (m, 2 H) 2.47 (m, 2 H) 1.88 (m, 4 H) 1.52 (m, 12 H) 1.30 (m, 1 H) 1.24 (m, 6 H) 0.92 (m, 10 H). ^{19}F NMR: δ ppm -68.68 (3F) -85.17 (3F). MS: MS *m/z* 902.9 (M^+-1).

Preparation of Compound 4349

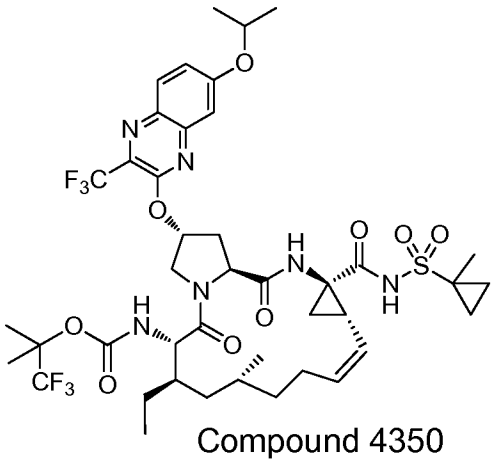


Compound 4349

Compound 4349 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4349: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.99 (m, 1 H) 7.92 (s, 1 H) 7.38 (m, 2 H) 6.00 (br. s., 1 H) 5.73 (m, 1 H) 5.07 (br. s., 1 H) 4.72 (dd, *J*=9.54, 7.03 Hz, 1 H) 4.61 (m, 1 H) 4.28 (q, *J*=7.19 Hz, 2 H) 4.11 (d, *J*=9.54 Hz, 1 H) 4.01 (s, 1 H) 3.37 (s, 1 H) 2.60 (m, 3 H) 2.02 (m, 2 H) 1.72 (m, 1 H) 1.56 (m, 9 H) 1.43 (m, 2 H) 1.29 (d, *J*=16.06 Hz, 8 H) 1.18 (d, *J*=10.04 Hz, 1 H) 1.07 (d, *J*=6.53 Hz, 3 H) 0.94 (m, 6 H). ^{19}F NMR: δ ppm -68.68 (3F) -85.11 (3F). MS: MS *m/z* 902.8 (M^{+}-1).

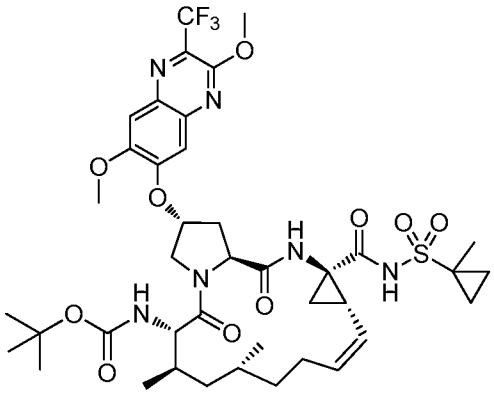
Preparation of Compound 4350



Compound 4350

Compound 4350 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4350: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-isopropoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.98 (d, *J*=9.04 Hz, 1 H) 7.30 - 7.39 (m, 2 H) 5.95 - 6.03 (m, 1 H) 5.57 - 5.67 (m, 1 H) 5.00 - 5.14 (m, 1 H) 4.80 (d, *J*=12.55 Hz, 1 H) 4.63 (dd, *J*=9.79, 7.28 Hz, 1 H) 3.94 - 4.10 (m, 2 H) 2.93 (br. s., 1 H) 2.72 (dt, *J*=13.80, 7.15 Hz, 2 H) 2.35 - 2.54 (m, 2 H) 1.98 (br. s., 2 H) 1.78 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.40 - 1.65 (m, 13 H) 1.17 - 1.36 (m, 10 H) 0.99 - 1.13 (m, 9 H) 0.74 - 0.84 (m, 3 H). MS: MS *m/z* 932.17 (M^++1).

Preparation of Compound 4351

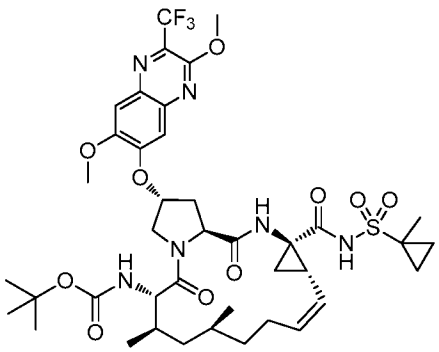


Compound 4351

Compound 4351 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001.

Compound 4351: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,7-dimethoxy-2-(trifluoromethyl)quinoxalin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.45 (d, *J*=11.55 Hz, 2 H) 5.62 (m, 1 H) 5.45 (br. s., 1 H) 4.99 (m, 1 H) 4.64 (m, 2 H) 4.24 (d, *J*=5.02 Hz, 1 H) 4.18 (s, 3 H) 4.06 (d, *J*=9.04 Hz, 1 H) 3.98 (m, 3 H) 3.88 (d, *J*=11.55 Hz, 1 H) 3.43 (s, 1 H) 2.74 (m, 2 H) 2.46 (m, 1 H) 2.00 (s, 1 H) 1.87 (br. s., 1 H) 1.77 (dd, *J*=8.53, 5.52 Hz, 2 H) 1.66 (d, *J*=9.54 Hz, 1 H) 1.58 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.53 (s, 4 H) 1.44 (m, 2 H) 1.31 (s, 1 H) 1.20 (br. s., 1 H) 1.15 (s, 7 H) 1.01 (m, 3 H) 0.96 (m, 3 H) 0.90 (s, 2 H) 0.83 (m, 1 H). ^{19}F NMR: δ ppm -68.86 (3F). MS: MS *m/z* 864.9 (M^+-1).

Preparation of Compound 4352

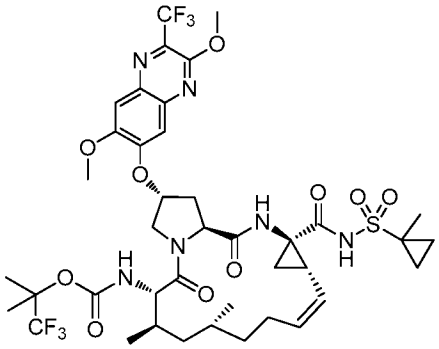


Compound 4352

Compound 4352 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001.

Compound 4352: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,7-dimethoxy-2-(trifluoromethyl)quinoxalin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.46 (d, *J*=15.56 Hz, 2 H) 5.75 (br. s., 1 H) 5.45 (br. s., 1 H) 5.06 (br. s., 1 H) 4.69 (t, *J*=8.53 Hz, 1 H) 4.57 (m, 1 H) 4.43 (m, 1 H) 4.18 (s, 5 H) 3.98 (s, 3 H) 3.44 (m, 1 H) 2.72 (m, 2 H) 2.49 (br. s., 1 H) 1.98 (d, *J*=19.07 Hz, 1 H) 1.73 (m, 1 H) 1.62 (br. s., 3 H) 1.52 (m, 4 H) 1.42 (m, 3 H) 1.31 (s, 1 H) 1.24 (s, 11 H) 1.15 (s, 1 H) 1.09 (d, *J*=6.53 Hz, 2 H) 0.95 (m, 11 H). ^{19}F NMR: δ ppm -68.88 (3F). MS: MS *m/z* 864.9 (M^+-1).

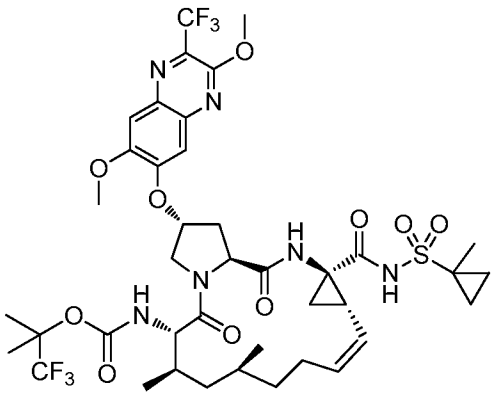
Preparation of Compound 4353



Compound 4353

Compound 4353 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4353: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,7-dimethoxy-2-(trifluoromethyl)quinoxalin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.46 (d, *J*=13.55 Hz, 2 H) 5.62 (br. s., 1 H) 5.46 (br. s., 1 H) 4.65 (m, 2 H) 4.18 (s, 3 H) 4.06 (dd, *J*=11.55, 2.51 Hz, 1 H) 3.98 (m, 3 H) 3.86 (d, *J*=11.04 Hz, 1 H) 3.40 (m, 1 H) 2.74 (m, 2 H) 2.46 (m, 2 H) 1.98 (t, *J*=6.53 Hz, 1 H) 1.78 (m, 1 H) 1.57 (m, 1 H) 1.46 (m, 6 H) 1.34 (m, 4 H) 1.24 (s, 3 H) 1.16 (s, 1 H) 0.94 (m, 11 H). ^{19}F NMR: δ ppm -68.87 (3F) -85.02 (3F). MS: MS *m/z* 918.9 (M^+-1).

Preparation of Compound 4354

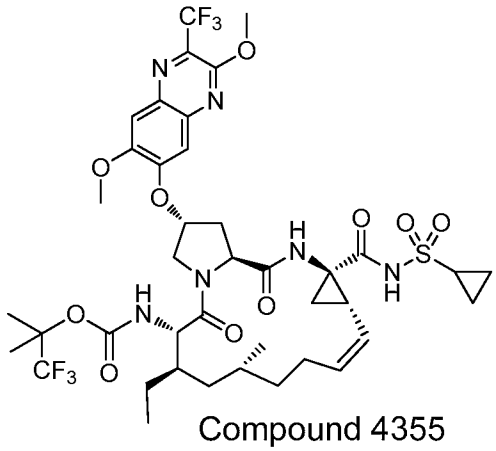


Compound 4354

Compound 4354 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4354: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,7-dimethoxy-2-(trifluoromethyl)quinoxalin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.44 (s, 2 H) 5.72 (d, *J*=9.04 Hz, 1 H) 5.42 (m, 1 H) 4.70 (dd, *J*=9.54, 7.03 Hz, 1 H) 4.58 (s, 1 H) 4.48 (d, *J*=11.55 Hz, 1 H) 4.15 (m, 5 H) 3.97 (m, 3 H) 2.72 (dd, *J*=14.31, 7.28 Hz, 1 H) 2.51 (m, 1 H) 2.01 (m, 2 H) 1.73 (dd, *J*=8.03, 5.52 Hz, 1 H) 1.61 (d, *J*=4.52 Hz, 3 H) 1.46 (m, 10 H) 1.33 (s, 6 H) 1.12 (m, 3 H) 0.94 (m, 5 H). ^{19}F NMR: δ ppm -68.88 (3F) -84.99 (3F). MS: MS *m/z* 919.0 (M^+-1).

Preparation of Compound 4355



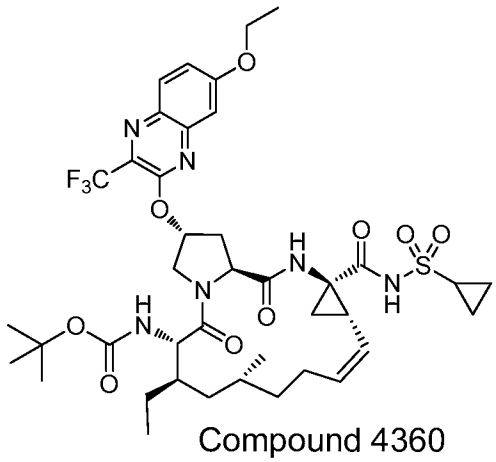
Compound 4355

Compound 4355 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4355: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3,7-dimethoxy-2-(trifluoromethyl)quinoxalin-6-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.46 (d, *J*=10.04 Hz, 2 H) 5.64 (m, 1 H) 5.45 (br. s., 1 H) 5.05 (t, *J*=9.79 Hz, 1 H) 4.74 (d, *J*=11.55 Hz, 1 H) 4.63 (dd, *J*=10.54, 7.03 Hz, 1 H) 4.24 (d, *J*=1.51 Hz, 1 H)

4.19 (s, 3 H) 4.07 (m, 2 H) 3.96 (s, 3 H) 2.95 (m, 1 H) 2.74 (m, 2 H) 2.44 (m, 2 H) 2.00 (m, 2 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.57 (m, 6 H) 1.34 (m, 6 H) 1.22 (m, 3 H) 1.08 (m, 6 H) 0.90 (m, 4 H). ^{19}F NMR: δ ppm -68.87 (3F) -85.0 (3F). MS: MS *m/z* 920.7 (M^++1).

Preparation of Compound 4360

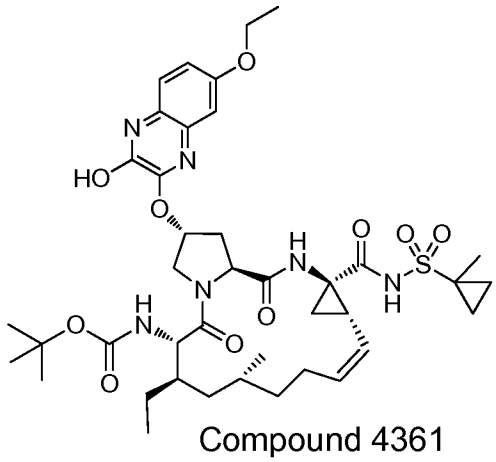


Compound 4360

Compound 4360 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001.

Compound 4360: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.97 (m, 1 H) 7.37 (m, 2 H) 6.01 (br. s., 1 H) 5.63 (m, 1 H) 5.05 (m, 1 H) 4.80 (d, *J*=12.05 Hz, 1 H) 4.62 (m, 1 H) 4.28 (m, 2 H) 4.05 (m, 2 H) 2.94 (br. s., 1 H) 2.70 (m, 2 H) 2.47 (m, 2 H) 1.97 (m, 2 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.56 (m, 9 H) 1.32 (m, 3 H) 1.09 (m, 15 H) 0.88 (m, 3 H). ^{19}F NMR: δ ppm -68.67 (3F). MS: MS *m/z* 848.9 (M^+-1).

Preparation of Compound 4361

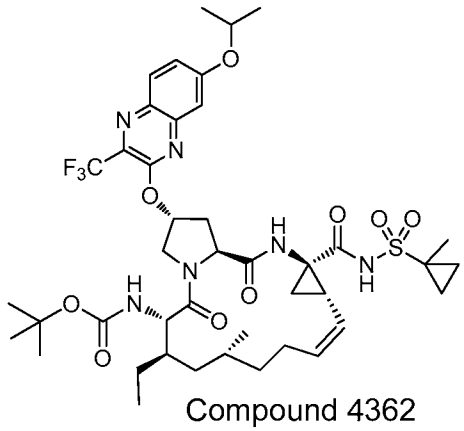


Compound 4361

Compound 4361 was isolated as by-product isolated in the preparation of Compound 4363; 3-chloro-6-ethoxy-2-(trifluoromethyl)quinoxaline was used as a reagent.

Compound 4361: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-ethoxy-3-hydroxyquinoxalin-2-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.19 (m, 2 H) 7.03 (m, 1 H) 6.60 (m, 1 H) 5.83 (br. s., 1 H) 5.63 (m, 1 H) 5.04 (br. s., 1 H) 4.96 (s, 0 H) 4.79 (s, 1 H) 4.82 (s, 1 H) 4.67 (dd, *J*=9.79, 7.28 Hz, 1 H) 4.09 (m, 3 H) 3.43 (s, 1 H) 2.69 (m, 2 H) 2.43 (m, 1 H) 1.97 (m, 2 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.67 (d, *J*=10.54 Hz, 1 H) 1.52 (m, 12 H) 1.29 (m, 2 H) 1.12 (m, 9 H) 1.00 (m, 3 H) 0.86 (m, 5 H). MS: MS *m/z* 810.9 (M^+-1).

Preparation of Compound 4362

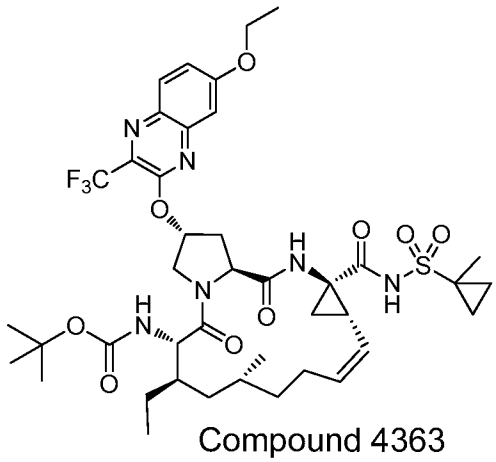


Compound 4362

Compound 4362 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001.

Compound 4362: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-isopropoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.96 (d, *J*=9.04 Hz, 1 H) 7.29 - 7.41 (m, 2 H) 5.94 - 6.07 (m, 1 H) 5.53 - 5.73 (m, 1 H) 4.64 (d, *J*=9.54 Hz, 1 H) 3.94 - 4.16 (m, 2 H) 2.63 - 2.85 (m, 2 H)) 2.37 - 2.57 (m, 2 H) 1.95 (br. s., 2 H) 1.61 - 1.86 (m, 3 H) 1.38 - 1.61 (m, 16 H) 1.22 - 1.38 (m, 5 H) 0.73 - 1.20 (m, 19 H). ^{19}F NMR: δ ppm -68.65 (3F). MS: MS *m/z* 876.9 (M^+-1).

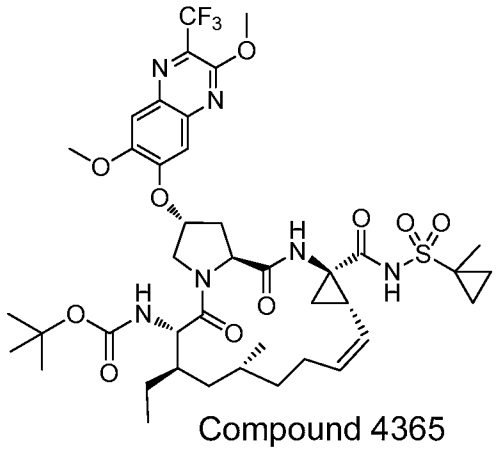
Preparation of Compound 4363



Compound 4363

Compound 4363 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001. Compound 4363: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.91 - 8.05 (m, 1 H) 7.28 - 7.43 (m, 2 H) 6.02 (br. s., 1 H) 5.56 - 5.72 (m, 1 H) 4.95 - 5.11 (m, 1 H) 4.74 - 4.83 (m, 1 H) 4.64 (dd, *J*=9.79, 6.78 Hz, 1 H) 4.19 - 4.36 (m, 2 H) 3.96 - 4.16 (m, 2 H) 2.64 - 2.83 (m, 2 H) 2.38 - 2.59 (m, 1 H) 1.86 - 2.13 (m, 1 H) 1.77 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.62 - 1.71 (m, 1 H) 1.43 - 1.60 (m, 12 H) 1.25 - 1.40 (m, 6 H) 1.03 - 1.21 (m, 9 H) 0.95 - 1.06 (m, 4 H) 0.76 - 0.97 (m, 6 H). ^{19}F NMR: δ ppm -68.67 (3F). MS: MS *m/z* 862.9 (M^+-1).

Preparation of Compound 4365

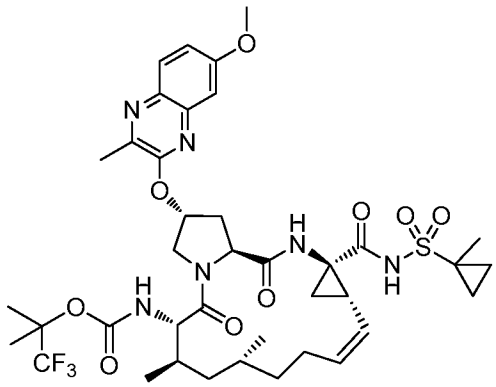


Compound 4365

Compound 4365 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001. Compound 4365: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,7-dimethoxy-2-(trifluoromethyl)quinoxalin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.09 (s, 1 H) 7.45 (d, *J*=6.71 Hz, 2 H) 5.63 (td, *J*=10.05, 5.62 Hz, 1 H) 5.45 (br. s., 1 H) 4.99 (m, 1 H) 4.75 (m, 1 H) 4.64 (m, 1 H) 4.18 (s, 3 H) 4.07 (m, 1 H) 3.96 (s, 2 H)

3.43 (t, *J*=1.66 Hz, 1 H) 2.74 (m, 2 H) 2.46 (m, 1 H) 1.77 (dd, *J*=8.41, 5.58 Hz, 1 H) 1.66 (m, 1 H) 1.49 (m, 8 H) 1.19 (m, 8 H) 1.01 (d, *J*=6.40 Hz, 2 H) 0.88 (m, 5 H). ^{19}F NMR: δ ppm -68.66 (3F). MS: MS *m/z* 878.9 (M^++1).

Preparation of Compound 4366

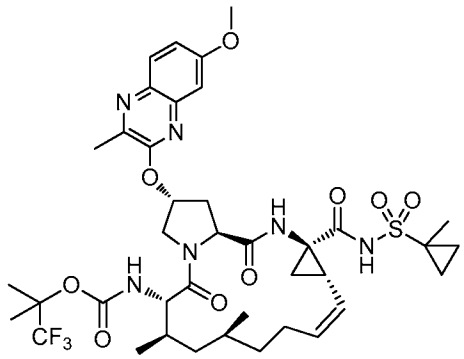


Compound 4366

Compound 4366 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4366: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.79 (d, *J*=9.04 Hz, 1 H) 7.30 (d, *J*=2.51 Hz, 1 H) 7.24 (m, 1 H) 5.91 (br. s., 1 H) 5.63 (d, *J*=5.52 Hz, 1 H) 4.75 (d, *J*=12.05 Hz, 1 H) 4.65 (m, 1 H) 4.06 (dd, *J*=11.80, 3.26 Hz, 1 H) 3.96 (m, 3 H) 3.78 (d, *J*=11.04 Hz, 1 H) 2.73 (m, 2 H) 2.53 (m, 3 H) 2.48 (m, 1 H) 2.42 (br. s., 1 H) 1.90 (m, 3 H) 1.78 (dd, *J*=8.53, 5.52 Hz, 2 H) 1.67 (d, *J*=11.04 Hz, 1 H) 1.58 (dd, *J*=9.54, 5.52 Hz, 1 H) 1.53 (s, 3 H) 1.49 (d, *J*=9.04 Hz, 2 H) 1.43 (m, 1 H) 1.30 (m, 7 H) 1.23 (br. s., 1 H) 1.00 (dd, *J*=14.31, 6.78 Hz, 7 H) 0.87 (m, 3 H). ^{19}F NMR: δ ppm -85.04 (3F). MS: MS *m/z* 834.9 (M^+-1).

Preparation of Compound 4367

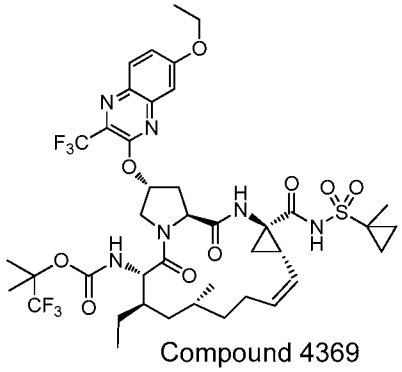


Compound 4367

Compound 4367 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4367: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.79 (d, *J*=9.04 Hz, 1 H) 7.30 (d, *J*=3.01 Hz, 1 H) 7.24 (dd, *J*=9.04, 3.01 Hz, 1 H) 5.94 (br. s., 1 H) 5.74 (m, 1 H) 5.05 (m, 1 H) 4.74 (dd, *J*=9.29, 7.28 Hz, 1 H) 4.53 (d, *J*=11.55 Hz, 1 H) 4.10 (m, 2 H) 3.96 (m, 3 H) 2.70 (m, 2 H) 2.50 (m, 5 H) 2.01 (m, 2 H) 1.75 (m, 1 H) 1.62 (m, 3 H) 1.48 (m, 6 H) 1.37 (m, 5 H) 1.26 (m, 2 H) 1.11 (d, *J*=7.03 Hz, 3 H) 1.00 (dd, *J*=13.80, 6.78 Hz, 1 H) 0.90 (m, 6 H). ^{19}F NMR: δ ppm -85.00 (3F). MS: MS *m/z* 834.8 (M^{+}-1).

Preparation of Compound 4369

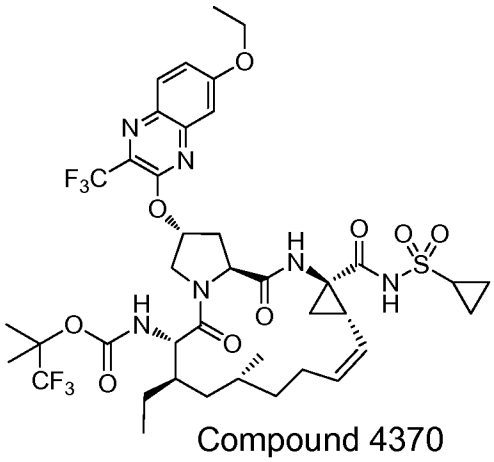


Compound 4369

Compound 4369 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4369: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.99 (d, *J*=10.04 Hz, 1 H) 7.38 (dq, *J*=5.02, 2.51 Hz, 2 H) 6.01 (br. s., 1 H) 5.63 (td, *J*=10.16, 6.27 Hz, 1 H) 5.01 (t, *J*=10.04 Hz, 1 H) 4.80 (d, *J*=11.55 Hz, 1 H) 4.65 (dd, *J*=10.29, 7.28 Hz, 1 H) 4.20 - 4.36 (m, 2 H) 3.92 - 4.15 (m, 2 H) 2.63 - 2.82 (m, 2 H) 2.32 - 2.60 (m, 2 H) 1.89 - 2.08 (m, 2 H) 1.77 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.63 - 1.71 (m, 1 H) 1.38 - 1.62 (m, 13 H) 1.16 - 1.38 (m, 9 H) 0.74 - 1.16 (m, 9 H). ^{19}F NMR: δ ppm -68.68 (3F) -85.13 (3F). MS: MS *m/z* 919.4 (M^++1).

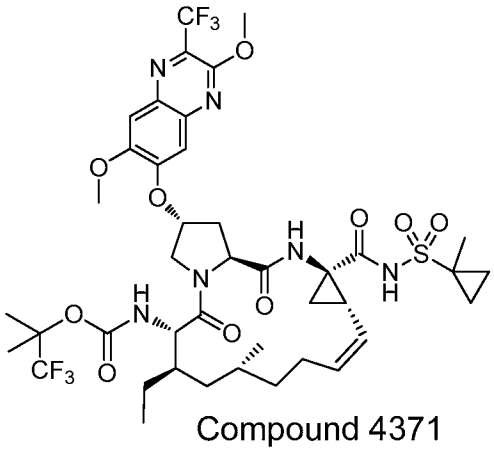
Preparation of Compound 4370



Compound 4370

Compound 4370 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4370: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.15 (s, 1 H) 7.99 (m, 1 H) 7.38 (m, 2 H) 6.00 (m, 1 H) 5.63 (td, *J*=10.16, 5.27 Hz, 1 H) 5.05 (t, *J*=9.79 Hz, 1 H) 4.80 (d, *J*=10.04 Hz, 1 H) 4.64 (dd, *J*=10.29, 6.78 Hz, 1 H) 4.29 (quind, *J*=6.90, 6.90, 6.90, 6.90, 2.51 Hz, 2 H) 4.03 (m, 2 H) 2.95 (tt, *J*=7.97, 4.83 Hz, 1 H) 2.71 (m, 2 H) 2.46 (m, 2 H) 1.98 (m, 2 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.55 (m, 8 H) 1.32 (m, 4 H) 1.10 (m, 8 H) 0.80 (t, *J*=7.53 Hz, 3 H). ^{19}F NMR: δ ppm -68.69 (3F) -85.14 (3F). MS: MS *m/z* 902.9 (M^{+}-1).

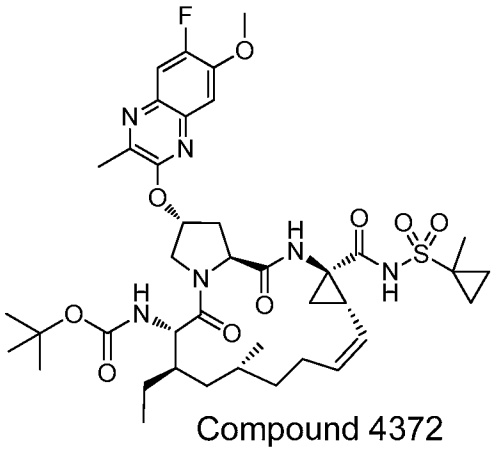
Preparation of Compound 4371



Compound 4371

Compound 4371 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4371: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,7-dimethoxy-2-(trifluoromethyl)quinoxalin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.09 (s, 1 H) 7.46 (d, *J*=10.04 Hz, 2 H) 5.63 (td, *J*=10.16, 5.77 Hz, 1 H) 5.46 (br. s., 1 H) 5.00 (m, 1 H) 4.75 (d, *J*=11.55 Hz, 1 H) 4.64 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.19 (s, 3 H) 4.07 (m, 2 H) 3.96 (s, 3 H) 2.75 (m, 2 H) 2.46 (ddd, *J*=13.80, 10.04, 4.27 Hz, 2 H) 2.01 (m, 2 H) 1.77 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.67 (m, 1 H) 1.56 (m, 7 H) 1.42 (m, 4 H) 1.28 (m, 4 H) 1.13 (t, *J*=11.80 Hz, 1 H) 1.01 (d, *J*=6.53 Hz, 3 H) 0.88 (m, 5 H). ^{19}F NMR: δ ppm -68.73 (3F) -85.0 (3F). MS: MS *m/z* 932.9 (M^{+}-1).

Preparation of Compound 4372

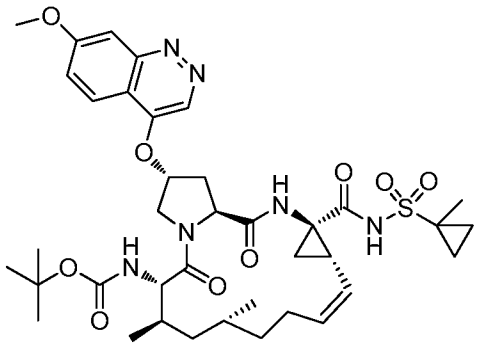


Compound 4372

Compound 4372 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4001.

Compound 4372: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-7-methoxy-3-methylquinoxalin-2-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm .99 (d, *J*=10.04 Hz, 1 H) 7.38 (dq, *J*=5.02, 2.51 Hz, 2 H) 6.01 (br. s., 1 H) 5.63 (td, *J*=10.16, 6.27 Hz, 1 H) 5.01 (t, *J*=10.04 Hz, 1 H) 4.80 (d, *J*=11.55 Hz, 1 H) 4.65 (dd, *J*=10.29, 7.28 Hz, 1 H) 4.20 - 4.36 (m, 2 H) 3.92 - 4.15 (m, 2 H) 2.63 - 2.82 (m, 2 H) 2.32 - 2.60 (m, 2 H) 1.89 - 2.08 (m, 2 H) 1.77 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.63 - 1.71 (m, 1 H) 1.38 - 1.62 (m, 13 H) 1.16 - 1.38 (m, 10 H) 0.74 - 1.16 (m, 10 H). ^{19}F NMR: δ ppm -131.26 (1F). MS: MS *m/z* 813.2 (M^{+}-1).

Preparation of Compound 4319

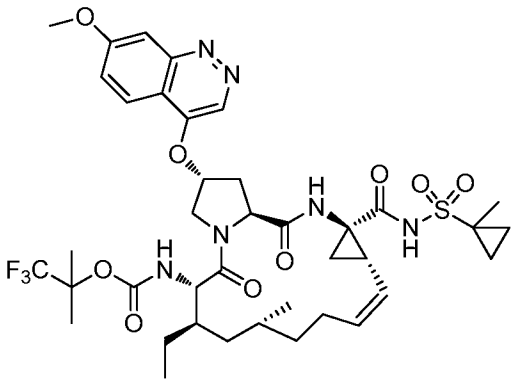


Compound 4319

Compound 4319 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4319 : tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-methoxycinnolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.09 (s, 1 H) 8.16 (d, *J*=9.04 Hz, 1 H) 7.64 (d, *J*=2.51 Hz, 1 H) 7.28 - 7.48 (m, 1 H) 6.70 (d, *J*=8.03 Hz, 1 H) 5.66 - 5.77 (m, 1 H) 5.56 - 5.67 (m, 1 H) 5.02 (t, *J*=10.29 Hz, 1 H) 4.64 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.10 (dd, *J*=12.05, 3.01 Hz, 1 H) 4.05 (s, 3 H) 3.70 - 3.87 (m, 1 H) 3.51 (t, *J*=3.39, 1.57 Hz, 1 H) 3.12 - 3.21 (m, 1 H) 2.82 (dd, *J*=13.05, 6.53 Hz, 1 H) 2.67 - 2.75 (m, 1 H) 2.53 (dd, *J*=13.93, 10.16, 4.02 Hz, 1 H) 2.41 (br. s., 1 H) 1.93 - 2.06 (m, 1 H) 1.72 - 1.83 (m, 2 H) 1.62 - 1.71 (m, 1 H) 1.54 - 1.59 (m, 1 H) 1.48 - 1.56 (m, 4 H) 1.38 - 1.48 (m, 2 H) 1.19 - 1.34 (m, 2 H) 1.08 (s, 8 H) 1.01 (dd, *J*=8.28, 6.78 Hz, 6 H) 0.83 - 0.96 (m, 4 H) 0.83 (s, 1 H). MS: MS *m/z* 769.4 (M^++1).

Preparation of Compound 4320

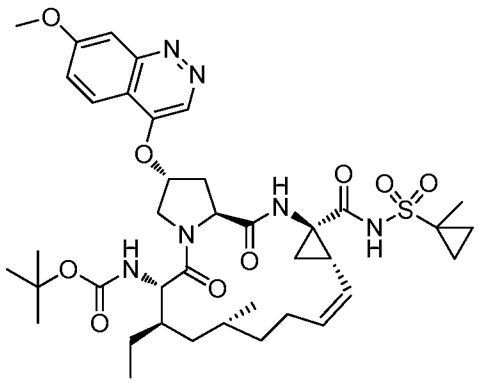


Compound 4320

Compound 4320 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3.

Compound 4320 : 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-methoxycinnolin-4-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 11.65 - 11.89 (m, 1 H) 10.01 (s, 1 H) 9.88 - 9.96 (m, 1 H) 8.72 - 8.91 (m, 1 H) 8.58 - 8.71 (m, 1 H) 8.45 - 8.59 (m, 1 H) 8.08 - 8.35 (m, 1 H) 6.46 - 6.59 (m, 1 H) 6.30 - 6.44 (m, 1 H) 5.69 - 5.96 (m, 1 H) 5.39 - 5.53 (m, 1 H) 5.25 - 5.35 (m, 1 H) 4.81 - 4.87 (m, 1 H) 4.74 - 4.79 (m, 1 H) 4.57 - 4.72 (m, 1 H) 4.05 (s, 3 H) 3.38 - 3.66 (m, 1 H) 3.00 - 3.22 (m, 1 H) 2.59 - 2.85 (m, 4 H) 2.40 - 2.50 (m, 9 H) 2.25 - 2.37 (m, 9 H) 2.23 (s, 3 H) 2.12 (s, 3 H) 1.81 (s, 2 H) 1.67 - 1.76 (m, 3 H) 1.43 - 1.60 (m, 2 H). MS: MS *m/z* 835.4 (M^+-1).

Preparation of Compound 4321

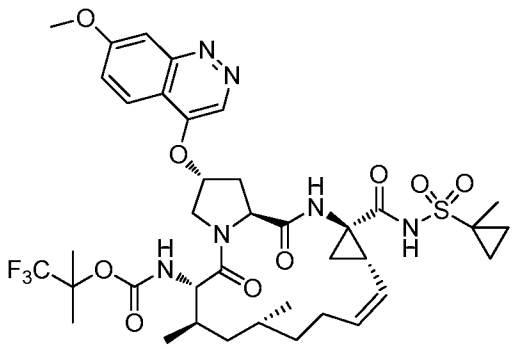


Compound 4321

Compound 4321 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4321 : tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-methoxycinnolin-4-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.08 (s, 1 H) 8.13 (d, *J*=9.29 Hz, 1 H) 7.61 (d, *J*=2.26 Hz, 1 H) 7.28 - 7.44 (m, 1 H) 5.67 - 5.72 (m, 1 H) 5.53 - 5.64 (m, 1 H) 5.00 (t, *J*=10.04 Hz, 1 H) 4.85 - 4.91 (m, 1 H) 4.62 (dd, *J*=10.16, 6.90 Hz, 1 H) 4.05 - 4.16 (m, 1 H) 3.98 - 4.07 (m, 4 H) 2.66 - 2.85 (m, 2 H) 2.35 - 2.55 (m, 2 H) 1.90 - 2.02 (m, 2 H) 1.76 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.54 - 1.69 (m, 3 H) 1.49 - 1.54 (m, 4 H) 1.34 - 1.43 (m, 2 H) 1.18 - 1.32 (m, 8 H) 1.09 - 1.16 (m, 1 H) 1.05 (s, 7 H) 1.00 (d, *J*=6.53 Hz, 3 H) 0.74 - 0.93 (m, 5 H). MS: MS *m/z* 783.8 (M^++1).

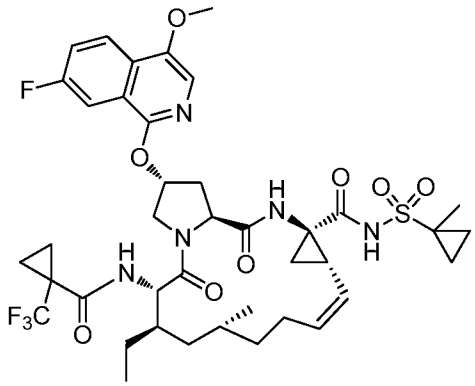
Preparation of Compound 4322



Compound 4322

Compound 4322 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4322: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-methoxycinnolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.25 (s, 1 H) 9.10 (s, 1 H) 8.28 (d, *J*=9.04 Hz, 1 H) 7.50 - 7.61 (m, 2 H) 7.11 (d, *J*=9.04 Hz, 1 H) 6.96 (d, *J*=2.01 Hz, 1 H) 5.89 (br. s., 1 H) 5.63 (dd, *J*=10.54, 5.52 Hz, 1 H) 4.56 - 4.77 (m, 1 H) 4.07 - 4.20 (m, 4 H) 3.98 (s, 1 H) 3.79 (d, *J*=11.55 Hz, 1 H) 3.50 (d, *J*=1.51 Hz, 1 H) 3.11 - 3.22 (m, 1 H) 2.89 (dd, *J*=15.06, 7.03 Hz, 1 H) 2.53 - 2.80 (m, 2 H) 1.79 (dd, *J*=7.78, 5.77 Hz, 1 H) 1.69 (s, 1 H) 1.60 (d, *J*=9.54 Hz, 1 H) 1.53 (s, 4 H) 1.26 - 1.41 (m, 9 H) 1.00 - 1.10 (m, 9 H) 0.84 - 0.94 (m, 3 H). MS: MS *m/z* 824.2(M^++1).

Preparation of Compound 4323

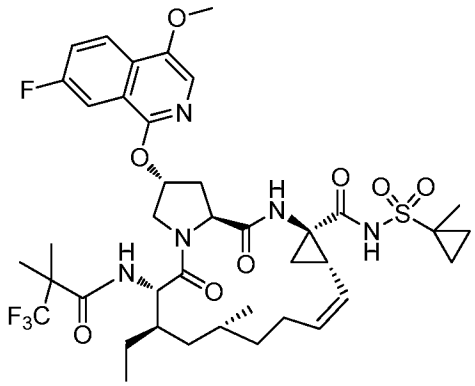


Compound 4323

Compound 4323 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4029.

Compound 4323 : (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-6-(1-(trifluoromethyl)cyclopropanecarboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.20 (dd, *J*=9.29, 5.27 Hz, 1 H) 7.71 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.47 - 7.62 (m, 2 H) 5.87 (br. s., 1 H) 5.54 - 5.71 (m, 1 H) 4.95 - 5.14 (m, 1 H) 4.57 - 4.76 (m, 2 H) 4.45 (d, *J*=11.04 Hz, 1 H) 4.04 (s, 4 H) 2.67 - 2.83 (m, 2 H) 2.43 (s, 2 H) 1.92 - 2.28 (m, 2 H) 1.72 - 1.85 (m, 1 H) 1.58 (dd, *J*=9.54, 5.52 Hz, 6 H) 1.53 (s, 4 H) 1.40 - 1.50 (m, 7 H) 1.29 (d, *J*=15.56 Hz, 2 H) 1.12 - 1.22 (m, 1 H) 1.09 (s, 1 H) 1.01 - 1.07 (m, 4 H) 0.90 (s, 2 H) 0.80 (s, 1 H). MS: MS *m/z* 835.8 (M^++1).

Preparation of Compound 4324

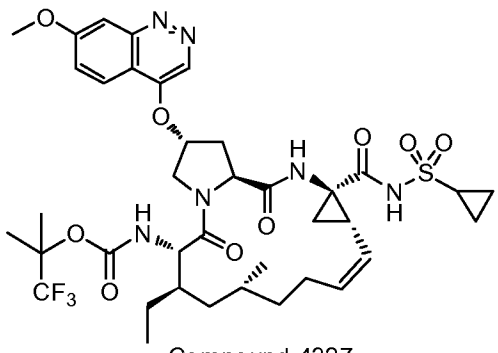


Compound 4324

Compound 4324 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 4029.

Compound 4324 : (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-6-(3,3,3-trifluoro-2,2-dimethylpropanamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.19 (dd, *J*=9.29, 5.27 Hz, 1 H) 7.72 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.48 - 7.63 (m, 2 H) 5.88 (s, 1 H) 5.50 - 5.71 (m, 1 H) 5.03 (t, *J*=9.79 Hz, 1 H) 4.73 (d, *J*=11.04 Hz, 1 H) 4.60 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.43 - 4.53 (m, 1 H) 3.97 - 4.10 (m, 4 H) 2.74 (t, *J*=8.03 Hz, 2 H) 2.19 (d, *J*=7.03 Hz, 1 H) 1.94 - 2.09 (m, 1 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.56 - 1.70 (m, 11 H) 1.52 - 1.56 (m, 4 H) 1.40 - 1.49 (m, 2 H) 1.27 - 1.36 (m, 2 H) 1.19 - 1.25 (m, 3 H) 1.12 - 1.19 (m, 2 H) 1.03 (d, *J*=6.53 Hz, 3 H) 0.88 - 1.00 (m, 2 H) 0.71 - 0.87 (m, 3 H). MS: MS *m/z* 837.8 (M^++1).

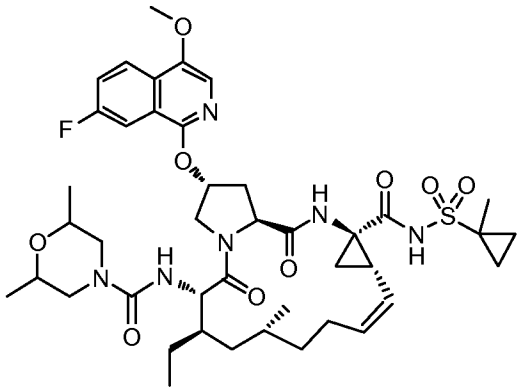
Preparation of Compound 4327



Compound 4327

Compound 4327 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3 Compound 4327: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-methoxycinnolin-4-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm9.11 (s, 1 H) 8.14 (s, 1 H) 7.66 (s, 1 H) 7.41 (dd, *J*=9.29, 2.26 Hz, 1 H) 5.70 (br. s., 1 H) 5.62 (d, *J*=6.02 Hz, 1 H) 4.65 (dd, *J*=10.29, 7.28 Hz, 1 H) 3.99 - 4.10 (m, 5 H) 2.94 (br. s., 1 H) 2.78 - 2.86 (m, 1 H) 2.70 (br. s., 1 H) 2.50 - 2.57 (m, 1 H) 2.41 (br. s., 1 H) 1.99 (br. s., 2 H) 1.76 - 1.81 (m, 1 H) 1.44 - 1.63 (m, 6 H) 1.27 - 1.34 (m, 5 H) 1.01 - 1.16 (m, 12 H) 0.92 (s, 3 H) 0.81 - 0.86 (m, 3 H). MS: MS *m/z* 823.2 (M^++1).

Preparation of Compound 4328

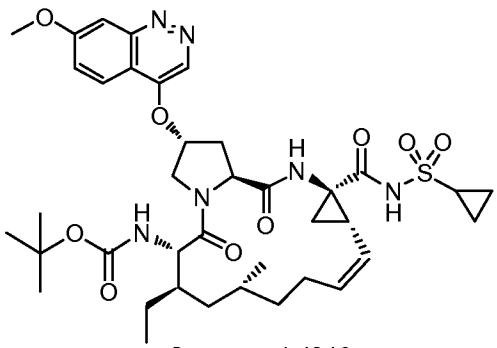


Compound 4328

Compound 4328 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4283. Compound 4328: N-((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-2,6-dimethylmorpholine-4-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.94 (d, *J*=5.77 Hz, 1 H) 7.86 (d, *J*=11.80 Hz, 1 H) 7.39 (s, 1 H) 7.30 (d, *J*=5.77 Hz, 1 H) 5.88 - 5.94 (m, 1 H) 5.64 (d, *J*=5.77 Hz, 1 H) 5.02

(t, *J*=10.04 Hz, 1 H) 4.77 (d, *J*=11.04 Hz, 1 H) 4.59 (dd, *J*=9.91, 7.15 Hz, 1 H) 4.29 (d, *J*=11.29 Hz, 1 H) 4.03 (s, 3 H) 3.99 (d, *J*=3.51 Hz, 1 H) 3.59 - 3.71 (m, 2 H) 3.34 - 3.46 (m, 3 H) 2.69 - 2.80 (m, 2 H) 2.37 - 2.53 (m, 2 H) 2.19 - 2.30 (m, 2 H) 2.05 (br. s., 2 H) 1.77 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.49 - 1.69 (m, 10 H) 1.20 - 1.47 (m, 5 H) 1.06 - 1.20 (m, 7 H) 1.02 (d, *J*=7.03 Hz, 3 H) 0.80 - 0.93 (m, 6 H). MS: MS *m/z* 840.9 (M^++1).

Preparation of Compound 4340

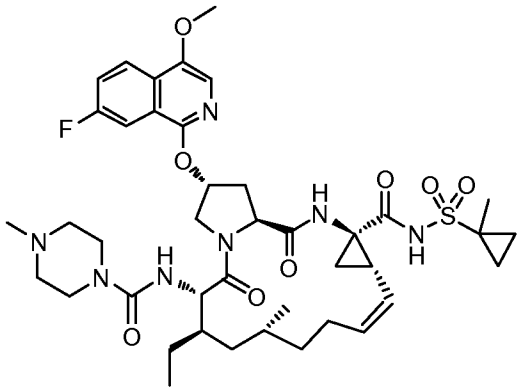


Compound 4340

Compound 4340 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001

Compound 4340: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-methoxycinnolin-4-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm9.09 (s, 1 H) 8.15 (s, 1 H) 7.92 (s, 1 H) 7.64 (s, 1 H) 7.35 - 7.41 (m, 1 H) 5.69 (br. s., 1 H) 5.59 - 5.65 (m, 1 H) 4.58 - 4.65 (m, 1 H) 4.02 - 4.12 (m, 4 H) 2.93 (br. s., 1 H) 2.81 (dd, *J*=13.55, 6.53 Hz, 1 H) 2.70 (d, *J*=16.06 Hz, 1 H) 2.48 - 2.57 (m, 1 H) 2.40 (d, *J*=13.05 Hz, 1 H) 1.91 - 2.03 (m, 2 H) 1.78 (dd, *J*=8.28, 5.27 Hz, 1 H) 1.50 - 1.64 (m, 5 H) 1.26 - 1.35 (m, 8 H) 0.93 - 1.17 (m, 16 H) 0.84 (t, *J*=7.53 Hz, 3 H). MS: MS *m/z* 769.4 (M^++1).

Preparation of Compound 4341



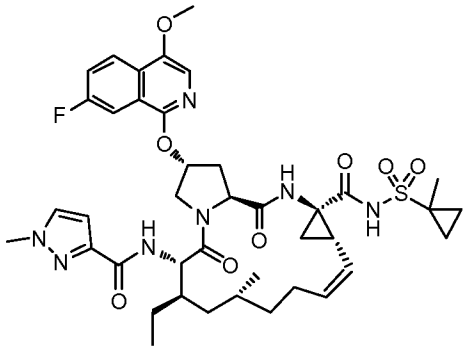
Compound 4341

Compound 4341 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4283.

Compound 4341: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-6-(4-methylpiperazine-1-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide.

^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.83 (br. s., 1 H) 8.44 - 8.52 (m, 1 H) 8.19 (dd, *J*=9.29, 5.27 Hz, 1 H) 7.97 (t, *J*=6.78 Hz, 1 H) 7.89 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.52 - 7.59 (m, 2 H) 5.86 (br. s., 1 H) 5.66 (s, 1 H) 4.97 - 5.05 (m, 1 H) 4.80 (s, 1 H) 4.53 - 4.59 (m, 1 H) 4.19 - 4.26 (m, 1 H) 4.01 - 4.06 (m, 3 H) 2.92 (s, 3 H) 2.70 - 2.80 (m, 2 H) 2.37 - 2.58 (m, 2 H) 1.91 - 2.09 (m, 1 H) 1.63 - 1.81 (m, 4 H) 1.42 - 1.56 (m, 6 H) 1.31 - 1.37 (m, 12 H) 1.17 - 1.23 (m, 3 H) 0.84 - 1.07 (m, 7 H). MS: MS *m/z* 826.6 (M^++1).

Preparation of Compound 4356



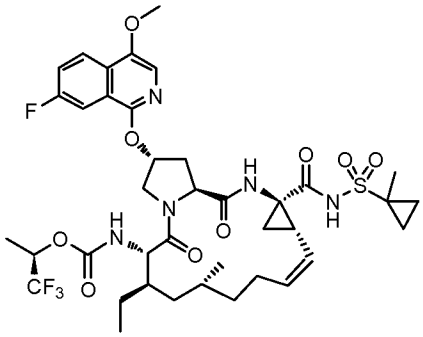
Compound 4356

Compound 4356 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4029.

Compound 4356: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-6-(1-methyl-1H-pyrazole-3-carboxamido)-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide.

^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.14 (dd, *J*=9.29, 5.27 Hz, 1 H) 7.92 (s, 2 H) 7.65 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.53 - 7.57 (m, 2 H) 7.48 (t, *J*=8.91, 2.76 Hz, 1 H) 6.44 (d, *J*=2.51 Hz, 1 H) 5.89 (br. s., 1 H) 5.66 (d, *J*=6.02 Hz, 1 H) 5.00 - 5.08 (m, 1 H) 4.73 (d, *J*=11.55 Hz, 1 H) 4.57 - 4.68 (m, 2 H) 4.08 - 4.13 (m, 1 H) 4.04 (s, 3 H) 3.91 (s, 3 H) 2.75 (d, *J*=18.07 Hz, 2 H) 2.41 - 2.50 (m, 2 H) 1.75 - 1.80 (m, 1 H) 1.52 - 1.71 (m, 9 H) 1.42 - 1.48 (m, 1 H) 1.31 (s, 2 H) 1.18 - 1.25 (m, 4 H) 1.04 (d, *J*=6.53 Hz, 3 H) 0.82 - 0.92 (m, 5 H). MS: MS *m/z* 808.4 (M^++1).

Preparation of Compound 4357

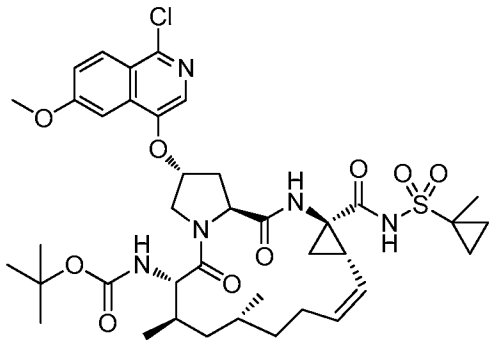


Compound 4357

Compound 4357 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 3117

Compound 4357: (R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.03 (s, 1 H) 8.18 (dd, *J*=9.29, 5.27 Hz, 1 H) 7.80 (dd, *J*=9.79, 2.76 Hz, 1 H) 7.50 - 7.61 (m, 3 H) 5.85 (t, *J*=3.01 Hz, 1 H) 5.59 - 5.67 (m, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.76 (d, *J*=11.55 Hz, 1 H) 4.54 - 4.66 (m, 1 H) 4.07 - 4.14 (m, 1 H) 3.98 - 4.04 (m, 4 H) 2.68 - 2.81 (m, 2 H) 2.43 (dd, *J*=13.93, 4.27 Hz, 2 H) 2.00 (d, *J*=8.53 Hz, 2 H) 1.76 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.48 - 1.69 (m, 9 H) 1.40 - 1.46 (m, 4 H) 1.12 - 1.24 (m, 3 H) 0.80 - 1.06 (m, 9 H). MS: MS *m/z* 837.9 (M^++1).

Preparation of Compound 4375



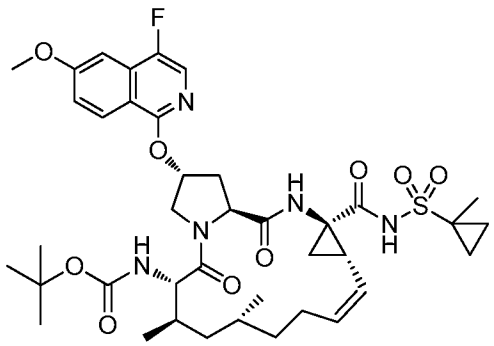
Compound 4375

Compound 4375 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4375 : tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((1-chloro-6-methoxyisoquinolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.05 - 9.13 (m, 1 H) 8.20 (d, *J*=9.04 Hz, 2 H) 7.87 (s, 2 H) 7.35 - 7.47 (m, 4 H) 5.63 (td, *J*=9.98, 5.65 Hz, 2 H) 5.50 (br. s., 2 H) 4.93 - 5.10 (m, 3 H) 4.76 (d, *J*=11.54 Hz, 2 H) 4.67 (dd, *J*=10.29, 7.03 Hz, 2 H) 4.00 - 4.07 (m, 2 H) 3.97 (s, 6 H) 3.86 (d,

J=10.79 Hz, 2 H) 3.50 (dt, *J*=3.33, 1.73 Hz, 1 H) 3.15 (dt, *J*=3.26, 1.63 Hz, 1 H) 2.67 - 2.75 (m, 1 H) 2.53 (dd, *J*=13.93, 10.16, 4.02 Hz, 1 H) 2.41 (br. s., 1 H) 1.93 - 2.06 (m, 1 H) 1.72 - 1.83 (m, 2 H) 1.62 - 1.71 (m, 1 H) 1.54 - 1.59 (m, 1 H) 1.48 - 1.56 (m, 4 H) 1.38 - 1.48 (m, 2 H) 1.19 - 1.34 (m, 2 H) 1.08 (s, 8 H) 1.01 (dd, *J*=8.28, 6.78 Hz, 6 H) 0.83 - 0.96 (m, 4 H) 0.83 (s, 1 H). MS: MS *m/z* 802.5(M^++1).

Preparation of Compound 4374

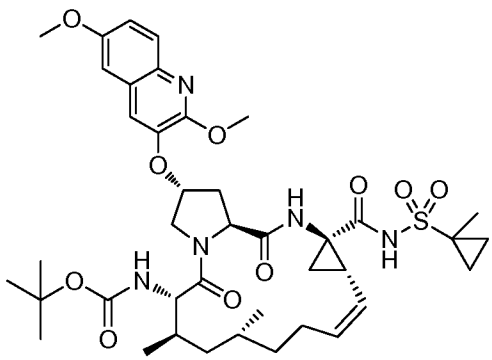


Compound 4374

Compound 4374 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4374: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-fluoro-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.03 (s, 1 H) 8.12 (dd, *J*=9.03, 1.76 Hz, 2 H) 7.83 (d, *J*=2.51 Hz, 2 H) 7.30 (d, *J*=2.26 Hz, 2 H) 7.19 (dd, *J*=9.16, 2.38 Hz, 1 H) 5.86 (br. s., 1 H) 5.62 (td, *J*=10.29, 5.52 Hz, 2 H) 4.92 - 5.06 (m, 2 H) 4.70 - 4.78 (m, 2 H) 4.62 (dd, *J*=9.79, 7.28 Hz, 1 H) 4.03 (dd, *J*=11.54, 3.26 Hz, 1 H) 3.96 - 4.00 (m, 5 H) 3.85 (d, *J*=10.79 Hz, 1 H) 3.50 (dt, *J*=3.33, 1.73 Hz, 1 H) 3.15 (dt, *J*=3.26, 1.63 Hz, 1 H) 2.67 - 2.75 (m, 1 H) 2.53 (dd, *J*=13.93, 10.16, 4.02 Hz, 1 H) 2.41 (br. s., 1 H) 1.93 - 2.06 (m, 1 H) 1.72 - 1.83 (m, 2 H) 1.62 - 1.71 (m, 1 H) 1.54 - 1.59 (m, 1 H) 1.48 - 1.56 (m, 4 H) 1.38 - 1.48 (m, 2 H) 1.19 - 1.34 (m, 2 H) 1.08 (s, 8 H) 1.01 (dd, *J*=8.28, 6.78 Hz, 6 H) 0.83 - 0.96 (m, 4 H) 0.83 (s, 1 H). MS: MS *m/z* 786.2 (M^++1).

Preparation of Compound 4373

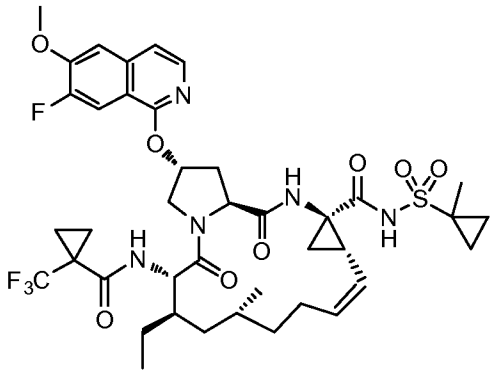


Compound 4373

Compound 4373 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4373: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,6-dimethoxyquinolin-3-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.07 (s, 1 H) 8.70 (d, *J*=2.51 Hz, 1 H) 8.02 - 8.07 (m, 1 H) 7.52 (s, 1 H) 7.35 (d, *J*=2.51 Hz, 1 H) 7.07 (dd, *J*=9.04, 2.51 Hz, 1 H) 6.52 (d, *J*=3.01 Hz, 1 H) 5.61 - 5.68 (m, 1 H) 5.00 (s, 1 H) 4.66 (dd, *J*=10.29, 6.78 Hz, 1 H) 4.06 - 4.14 (m, 1 H) 4.50 - 4.65 (m, 3 H) 3.98 - 4.05 (m, 3 H) 3.98 (br. s., 2 H) 3.12 - 3.18 (m, 1 H) 2.85 (dd, *J*=13.80, 6.78 Hz, 1 H) 2.70 - 2.76 (m, 1 H) 2.50 - 2.58 (m, 1 H) 2.43 (d, *J*=13.05 Hz, 1 H) 2.01 (br. s., 1 H) 1.78 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.51 - 1.69 (m, 8 H) 1.37 - 1.45 (m, 9 H) 1.15 - 1.22 (m, 12 H) 1.07 - 1.13 (m, 2 H) 0.81 - 0.92 (m, 4 H). MS: MS *m/z* 796.2 (M^++1).

Preparation of Compound 4331

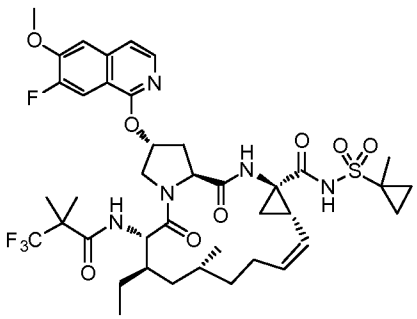


Compound 4331

Compound 4331 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4029.

Compound 4331: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-6-(1-(trifluoromethyl)cyclopropanecarboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.95 (d, *J*=6.02 Hz, 1 H) 7.75 (d, *J*=12.05 Hz, 1 H) 7.41 (d, *J*=8.03 Hz, 1 H) 7.31 (d, *J*=5.52 Hz, 1 H) 5.91 (t, *J*=3.26 Hz, 1 H) 5.64 (d, *J*=5.52 Hz, 1 H) 4.99 - 5.07 (m, 1 H) 4.68 (d, *J*=11.04 Hz, 1 H) 4.60 (dd, *J*=10.04, 7.03 Hz, 1 H) 4.46 (dd, *J*=11.04, 8.53 Hz, 1 H) 4.06 (d, *J*=3.51 Hz, 1 H) 4.03 (s, 3 H) 2.66 - 2.79 (m, 2 H) 2.39 - 2.50 (m, 2 H) 1.97 - 2.18 (m, 2 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.54 - 1.69 (m, 6 H) 1.37 - 1.54 (m, 6 H) 1.06 - 1.23 (m, 4 H) 1.03 (d, *J*=6.53 Hz, 3 H) 0.86 - 0.97 (m, 3 H) 0.83 (t, *J*=7.28 Hz, 3 H). MS: MS *m/z* 836.4 (M^++1).

Preparation of Compound 4332



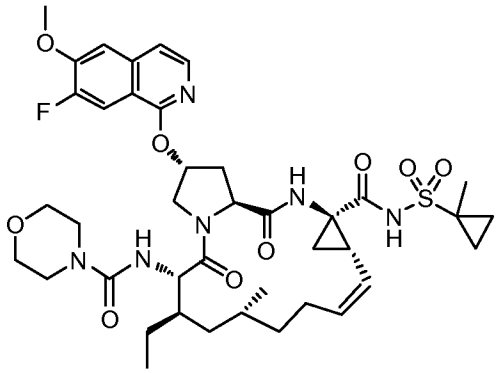
Compound 4332

Compound 4332 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4029.

Compound 4332: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-6-(3,3,3-trifluoro-2,2-dimethylpropanamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide.

^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.95 (d, *J*=5.77 Hz, 1 H) 7.74 (s, 1 H) 7.40 (d, *J*=8.28 Hz, 1 H) 7.32 (s, 1 H) 5.92 (t, *J*=3.14 Hz, 1 H) 5.61 - 5.67 (m, 1 H) 5.03 (t, *J*=10.04 Hz, 1 H) 4.74 (s, 1 H) 4.57 - 4.61 (m, 1 H) 4.49 (d, *J*=2.76 Hz, 1 H) 4.06 (d, *J*=7.78 Hz, 1 H) 4.03 (s, 3 H) 2.75 (d, *J*=9.29 Hz, 2H) 2.40 - 2.49 (m, 2 H) 2.02 (br. s., 1 H) 1.77 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.64 - 1.68 (m, 1 H) 1.47 - 1.60 (m, 10 H) 1.15 - 1.34 (m, 9 H) 1.03 (d, *J*=6.78 Hz, 3 H) 0.88 - 0.92 (m, 2 H) 0.78 - 0.82 (m, 3H). MS: MS *m/z* 838.2 (M^++1).

Preparation of Compound 4333



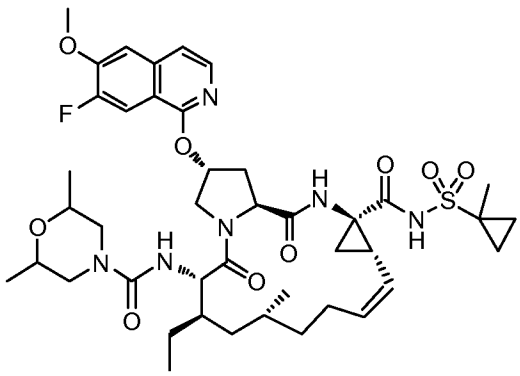
Compound 4333

Compound 4333 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4283.

Compound 4333: N-((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)morpholine-4-carboxamide. ^{1}H NMR (400 MHz,

CD_3OD): δ ppm 7.94 (d, *J*=6.02 Hz, 1 H) 7.88 (s, 1 H) 7.40 (d, *J*=8.28 Hz, 1 H) 7.29 (s, 1 H) 5.90 (br. s., 1 H) 5.63 (d, *J*=4.77 Hz, 1 H) 5.03 (br. s., 1 H) 4.81 (s, 1 H) 4.57 - 4.61 (m, 1 H) 4.28 - 4.33 (m, 1 H) 4.03 (s, 3 H) 4.01 (m, 1 H) 3.49 - 3.59 (m, 4H) 3.21 (ddd, *J*=10.60, 6.21, 3.76 Hz, 4 H) 2.75 (d, *J*=6.53 Hz, 2 H) 2.41 - 2.48 (m, 2 H) 1.96 - 2.08 (m, 2 H) 1.77 (d, *J*=2.76 Hz, 1 H) 1.60 - 1.68 (m, 3 H) 1.49 - 1.58 (m, 6 H) 1.40 - 1.47 (m, 2 H) 1.24 - 1.36 (m, 2 H) 1.17 (br. s., 1 H) 1.03 (d, *J*=6.78 Hz, 3 H) 0.80 - 0.94 (m, 5 H). MS: MS *m/z* 813.4 (M^++1).

Preparation of Compound 4334

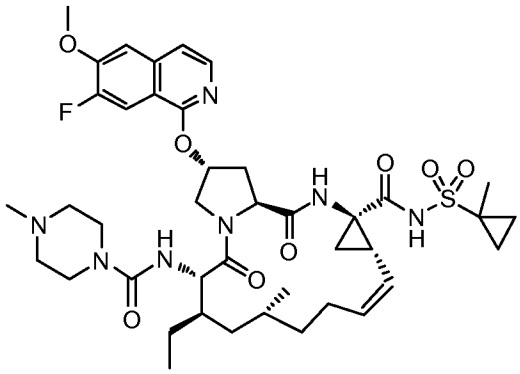


Compound 4334

Compound 4334 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4283.

Compound 4334: N-((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-2,6-dimethylmorpholine-4-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.94 (d, *J*=5.77 Hz, 1 H) 7.86 (d, *J*=11.80 Hz, 1 H) 7.39 (s, 1 H) 7.30 (d, *J*=5.77 Hz, 1 H) 5.88 - 5.94 (m, 1 H) 5.64 (d, *J*=5.77 Hz, 1 H) 5.02 (t, *J*=10.04 Hz, 1 H) 4.77 (d, *J*=11.04 Hz, 1 H) 4.59 (dd, *J*=9.91, 7.15 Hz, 1 H) 4.29 (d, *J*=11.29 Hz, 1 H) 4.03 (s, 3 H) 3.99 (d, *J*=3.51 Hz, 1 H) 3.59 - 3.71 (m, 2 H) 3.34 - 3.46 (m, 3 H) 2.69 - 2.80 (m, 2 H) 2.37 - 2.53 (m, 2 H) 2.19 - 2.30 (m, 2 H) 2.05 (br. s., 2 H) 1.77 (dd, *J*=8.41, 5.65 Hz, 1 H) 1.49 - 1.69 (m, 10 H) 1.20 - 1.47 (m, 5 H) 1.06 - 1.20 (m, 7 H) 1.02 (d, *J*=7.03 Hz, 3 H) 0.80 - 0.93 (m, 6 H). MS: MS *m/z* 841.4 (M^++1).

Preparation of Compound 4335

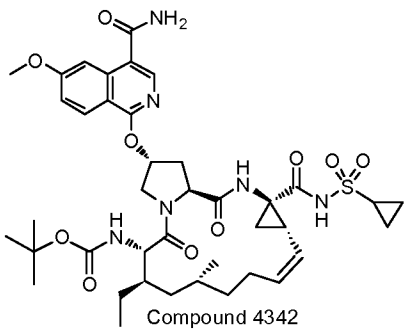


Compound 4335

Compound 4335 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4283.

Compound 4335: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-6-(4-methylpiperazine-1-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.91 - 7.98 (m, 2 H) 7.41 (d, *J*=8.28 Hz, 1 H) 7.31 (d, *J*=5.52 Hz, 1 H) 5.89 (br. s., 1 H) 5.65 (d, *J*=5.52 Hz, 1 H) 4.99 - 5.06 (m, 1 H) 4.79 (dd, *J*=10.79, 0.75 Hz, 1 H) 4.54 (dd, *J*=9.79, 7.28 Hz, 1 H) 4.26 (d, *J*=11.29 Hz, 1 H) 4.02 - 4.07 (m, 4 H) 3.37 (s, 2 H) 2.93 (s, 3 H) 2.69 - 2.81 (m, 3 H) 2.39 - 2.56 (m, 2 H) 1.90 - 2.13 (m, 2 H) 1.59 - 1.81 (m, 5 H) 1.39 - 1.56 (m, 8 H) 1.15 - 1.35 (m, 3 H) 1.04 (d, *J*=7.03 Hz, 3 H) 0.83 - 0.97 (m, 6 H). MS: MS *m/z* 826.5 (M^++1).

Preparation of Compound 4342

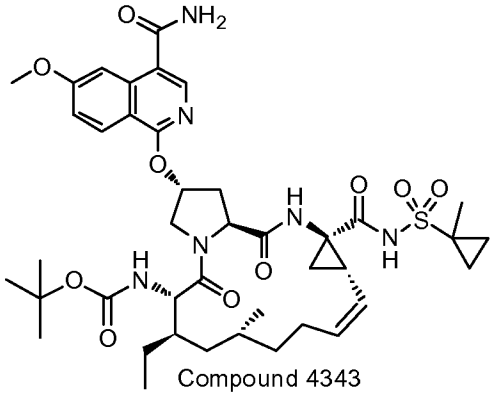


Compound 4342

Compound 4342 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001

Compound 4342: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-carbamoyl-6-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.83 (br. s., 1 H) 8.44 - 8.52 (m, 1 H) 8.19 (dd, *J*=9.29, 5.27 Hz, 1 H) 7.97 (t, *J*=6.78 Hz, 1 H) 7.89 (dd, *J*=9.54, 2.51 Hz, 1 H) 7.52 - 7.59 (m, 2 H) 5.86 (br. s., 1 H) 5.66 (s, 1 H) 4.97 - 5.05 (m, 1 H) 4.80 (s, 1 H) 4.53 - 4.59 (m, 1 H) 4.19 - 4.26 (m, 1 H) 4.01 - 4.06 (m, 3 H) 2.92 (s, 3 H) 2.70 - 2.80 (m, 2 H) 2.37 - 2.58 (m, 2 H) 1.91 - 2.09 (m, 1 H) 1.63 - 1.81 (m, 4 H) 1.42 - 1.56 (m, 6 H) 1.31 - 1.37 (m, 12 H) 1.17 - 1.23 (m, 3 H) 0.84 - 1.07 (m, 7 H). MS: MS *m/z* 811.2 (M^++1).

Preparation of Compound 4343

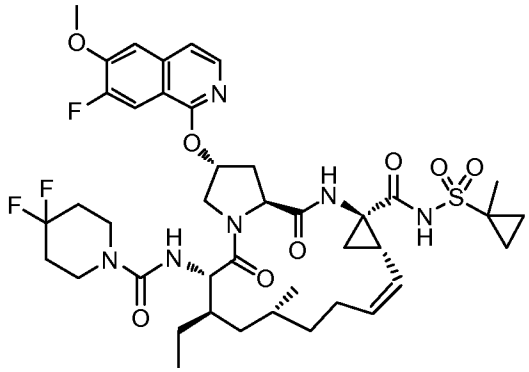


Compound 4343

Compound 4343 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4343: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-carbamoyl-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, DMSO-d_6) ppm 8.31 (s, 1 H) 8.08 (d, *J*=9.04 Hz, 1 H) 7.98 (d, *J*=2.51 Hz, 1 H) 7.41 (br. s., 1 H) 7.12 - 7.22 (m, 2 H) 5.89 (br. s., 1 H) 5.53 (d, *J*=5.52 Hz, 1 H) 4.96 (t, *J*=10.04 Hz, 1 H) 4.62 (d, *J*=11.04 Hz, 1 H) 4.49 (dd, *J*=10.29, 7.28 Hz, 1 H) 3.91 - 3.96 (m, 1 H) 3.88 (s, 3 H) 2.65 - 2.74 (m, 1 H) 2.57 - 2.65 (m, 1 H) 2.27 - 2.37 (m, 2 H) 1.92 (d, *J*=11.55 Hz, 2 H) 1.61 (dd, *J*=8.03, 5.52 Hz, 1 H) 1.50 (dd, *J*=9.29, 5.27 Hz, 2 H)

1.33 - 1.47 (m, 7 H) 1.23 - 1.32 (m, 2 H) 1.14 (s, 9 H) 1.02 (d, *J*=11.55 Hz, 2 H) 0.87 - 0.96 (m, 5 H) 0.73 (d, *J*=14.56 Hz, 3 H). MS: MS *m/z* 825.3 (M^++1).

Preparation of Compound 4344

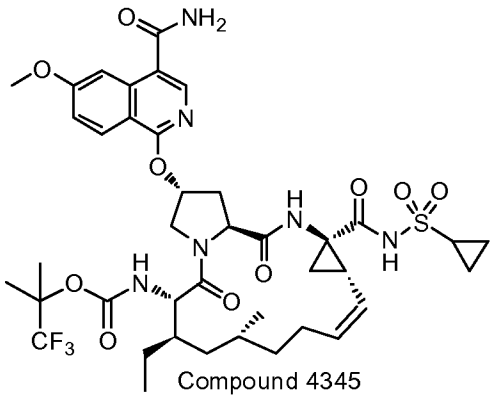


Compound 4344

Compound 4344 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 3117

Compound 4344: (2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(4,4-difluoropiperidine-1-carboxamido)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.00 (d, *J*=6.02 Hz, 1 H) 7.94 (dd, *J*=6.02, 3.01 Hz, 1 H) 7.86 (d, *J*=2.01 Hz, 1 H) 7.39 (d, *J*=8.03 Hz, 1 H) 7.29 (s, 1 H) 5.90 (d, *J*=4.02 Hz, 1 H) 5.58 - 5.67 (m, 1 H) 5.03 (t, *J*=10.04 Hz, 1 H) 4.80 (s, 1 H) 4.52 - 4.61 (m, 1 H) 4.30 (dd, *J*=16.31, 11.29 Hz, 1 H) 3.99 - 4.09 (m, 4 H) 3.49 - 3.61 (m, 2 H) 3.14 - 3.26 (m, 2 H) 2.68 - 2.81 (m, 2 H) 2.40 - 2.51 (m, 2 H) 2.20 - 2.32 (m, 2 H) 2.02 (d, *J*=18.07 Hz, 1 H) 1.78 (ddd, *J*=8.53, 5.52, 3.01 Hz, 1 H) 1.36 - 1.69 (m, 13 H) 1.18 (d, *J*=7.53 Hz, 1 H) 1.03 (dd, *J*=6.78, 3.26 Hz, 3 H) 0.79 - 0.92 (m, 5 H). MS: MS *m/z* 847.5(M^++1).

Preparation of Compound 4345

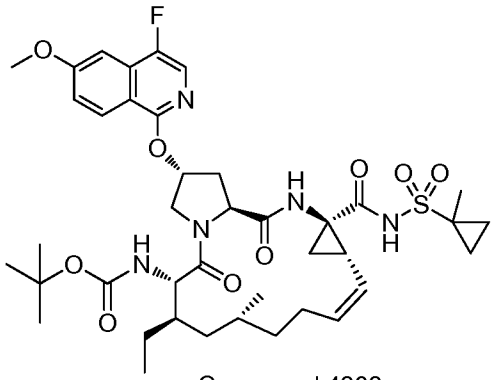


Compound 4345

Compound 4345 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3

Compound 4345: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-carbamoyl-6-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 11.16 (s, 1 H) 9.02 (s, 1 H) 8.32 (s, 1 H) 8.06 (d, *J*=9.04 Hz, 1 H) 7.98 (d, *J*=2.51 Hz, 2 H) 7.86 (d, *J*=8.03 Hz, 1 H) 7.43 (br. s., 1 H) 7.15 - 7.25 (m, 1 H) 5.88 (br. s., 1 H) 5.44 - 5.60 (m, 1 H) 5.04 (t, *J*=9.54 Hz, 1 H) 4.48 - 4.59 (m, 2 H) 3.81 - 4.00 (m, 5 H) 2.86 - 2.98 (m, 1 H) 2.56 - 2.70 (m, 2 H) 2.26 - 2.37 (m, 1 H) 1.92 (br. s., 2 H) 1.28 - 1.64 (m, 10 H) 0.88 - 1.22 (m, 11 H) 0.73 (t, *J*=7.28 Hz, 3 H). MS: MS *m/z* 865.2 (M^++1).

Preparation of Compound 4383

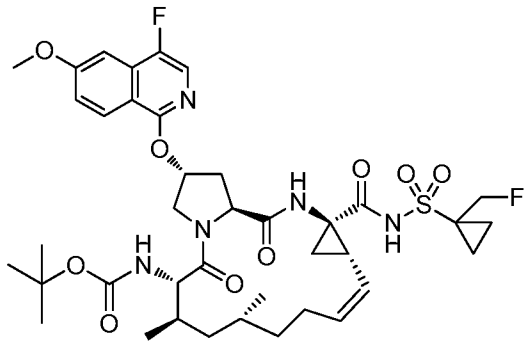


Compound 4383

Compound 4383 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4383: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((4-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.12 (dd, *J*=9.54, 2.01 Hz, 1 H) 7.84 (d, *J*=2.51 Hz, 1 H) 7.30 (d, *J*=2.51 Hz, 1 H) 7.21 (s, 1 H) 5.87 (br. s., 1 H) 5.59 - 5.67 (m, 1 H) 5.01 (s, 1 H) 4.71 - 4.81 (m, 1 H) 4.59 - 4.68 (m, 1 H) 4.02 (br. s., 2 H) 3.98 (s, 3 H) 2.68 - 2.80 (m, 2 H) 2.36 - 2.50 (m, 2 H) 1.97 (d, *J*=13.55 Hz, 2 H) 1.77 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.62 - 1.70 (m, 1 H) 1.57 (dd, *J*=10.29, 4.77 Hz, 7 H) 1.44 (dd, *J*=9.79, 4.27 Hz, 2 H) 1.31 (s, 1 H) 1.07 - 1.18 (m, 9 H) 1.02 (d, *J*=6.53 Hz, 3 H) 0.81 - 0.94 (m, 5 H). MS: MS *m/z* 800.4(M^++1).

Preparation of Compound 4382



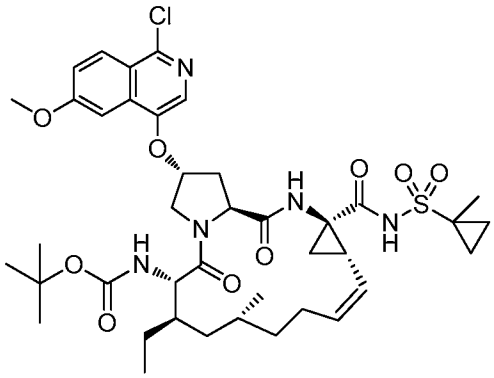
Compound 4382

Compound 4382 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4382: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.01 (s, 1 H) 8.13 (dd, *J*=9.04, 2.01 Hz, 1 H) 7.84 (d, *J*=2.51 Hz, 1 H) 7.30 (d, *J*=2.51

Hz, 1 H) 7.19 (dd, *J*=9.04, 2.51 Hz, 1 H) 5.86 (br. s., 1 H) 5.62 (td, *J*=10.29, 5.52 Hz, 1 H) 4.88 - 5.04 (m, 2 H) 4.70 - 4.81 (m, 1 H) 4.49 - 4.66 (m, 2 H) 4.02 - 4.09 (m, 1 H) 3.98 (s, 3 H) 3.86 (d, *J*=10.54 Hz, 1 H) 2.66 - 2.80 (m, 2 H) 2.37 - 2.50 (m, 2 H) 1.97 (br. s., 1 H) 1.62 - 1.89 (m, 5 H) 1.37 - 1.61 (m, 3 H) 1.19 - 1.34 (m, 3 H) 1.15 (s, 9 H) 0.96 - 1.05 (m, 6 H) 0.84 (t, *J*=12.80 Hz, 1 H). MS: MS *m/z* 804.2 (M^++1).

Preparation of Compound 4381

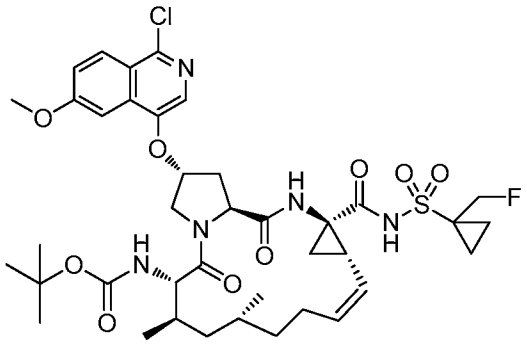


Compound 4381

Compound 4381 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4381: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((1-chloro-6-methoxyisoquinolin-4-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.10 (s, 1 H) 8.21 (d, *J*=9.04 Hz, 1 H) 7.88 (s, 1 H) 7.39 - 7.47 (m, 2 H) 5.58 - 5.71 (m, 1 H) 5.50 (br. s., 1 H) 5.01 (s, 1 H) 4.75 - 4.83 (m, 1 H) 4.64 - 4.73 (m, 1 H) 4.02 - 4.14 (m, 1 H) 3.98 (s, 3 H) 2.66 - 2.84 (m, 2 H) 2.36 - 2.52 (m, 2 H) 1.98 (d, *J*=12.05 Hz, 2 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.67 (d, *J*=10.04 Hz, 1 H) 1.20 - 1.60 (m, 12 H) 1.19 - 1.46 (m, 3 H) 1.08 - 1.18 (m, 2 H) 0.86 - 0.94 (m, 3 H) 0.84 (t, *J*=7.53 Hz, 2 H). MS: MS *m/z* 816.4 (M^++1).

Preparation of Compound 4380

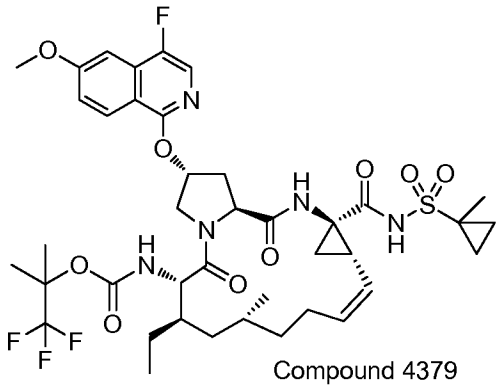


Compound 4380

Compound 4380 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4380 : tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((1-chloro-6-methoxyisoquinolin-4-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.21 (d, *J*=9.04 Hz, 1 H) 7.87 (s, 1 H) 7.36 - 7.47 (m, 2 H) 5.63 (d, *J*=5.52 Hz, 1 H) 5.50 (br. s., 1 H) 4.92 - 5.04 (m, 1 H) 4.72 - 4.80 (m, 1 H) 4.48 - 4.69 (m, 2 H) 4.04 (dd, *J*=12.05, 3.01 Hz, 1 H) 3.98 (s, 3 H) 3.86 (d, *J*=10.54 Hz, 1 H) 2.63 - 2.82 (m, 2 H) 2.34 - 2.52 (m, 2 H) 1.98 (br. s., 1 H) 1.76 - 1.90 (m, 2 H) 1.61 - 1.75 (m, 3 H) 1.39 - 1.59 (m, 3 H) 1.12 - 1.36 (m, 6 H) 1.01 - 1.08 (m, 11 H) 0.92 - 0.99 (m, 3 H) 0.84 (t, *J*=12.80 Hz, 1 H). MS: MS *m/z* 820.5(M^++1).

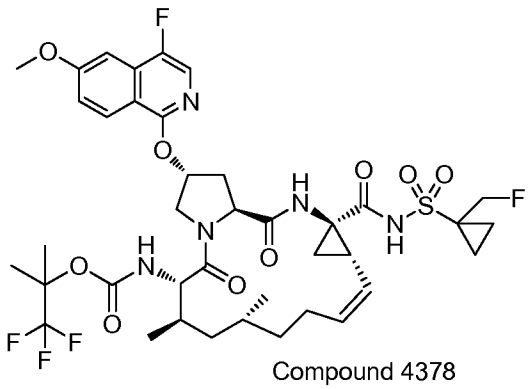
Preparation of Compound 4379



Compound 4379

Compound 4379 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3. Compound 4379 : 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((4-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.06 (s, 1 H) 8.11 (dd, *J*=9.04, 2.01 Hz, 1 H) 7.86 (d, *J*=2.51 Hz, 1 H) 7.32 (d, *J*=2.01 Hz, 1 H) 7.22 (dd, *J*=9.04, 2.51 Hz, 1 H) 5.87 (d, *J*=7.03 Hz, 1 H) 5.63 (d, *J*=6.02 Hz, 1 H) 4.97 - 5.04 (m, 1 H) 4.77 (s, 1 H) 4.62 - 4.68 (m, 1 H) 4.01 - 4.08 (m, 2 H) 3.99 (s, 3 H) 2.67 - 2.79 (m, 2 H) 2.44 (ddd, *J*=13.80, 10.04, 4.27 Hz, 2 H) 1.99 (br. s., 2 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.64 - 1.69 (m, 1 H) 1.54 - 1.61 (m, 4 H) 1.50 (br. s., 2 H) 1.36 - 1.44 (m, 4 H) 1.22 - 1.32 (m, 1 H) 1.09 - 1.16 (m, 1 H) 1.02 (d, *J*=7.03 Hz, 6 H) 0.89 - 0.94 (m, 2 H) 0.79 - 0.87 (m, 3 H). MS: MS *m/z* 854.5 (M^++1).

Preparation of Compound 4378

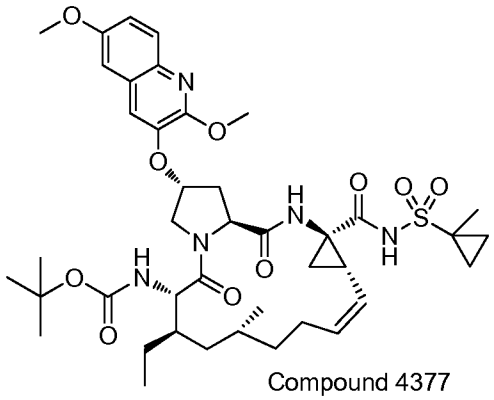


Compound 4378

Compound 4378 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of compound 3. Compound 4378 : 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.10 (s, 1 H) 8.22 (s, 1 H) 7.88 (s, 1 H) 7.38 - 7.47 (m, 2 H) 5.58 - 5.68 (m, 1 H) 5.50 (br. s., 1 H) 4.98 - 5.05 (m, 1 H) 4.77 - 4.82 (m, 1 H) 4.63 - 4.70 (m, 1 H) 4.02 - 4.09

(m, 1 H) 3.98 (s, 3 H) 2.69 - 2.83 (m, 2 H) 2.47 (ddd, *J*=13.93, 10.16, 3.51 Hz, 2 H) 1.98 (d, *J*=12.05 Hz, 2 H) 1.78 (dd, *J*=8.28, 5.77 Hz, 1 H) 1.62 - 1.70 (m, 1 H) 1.56 (dd, *J*=9.54, 5.52 Hz, 8 H) 1.51 (br. s., 3 H) 1.43 (dd, *J*=9.29, 4.77 Hz, 2 H) 1.20 - 1.34 (m, 2 H) 1.07 - 1.16 (m, 2 H) 0.88 - 0.93 (m, 2 H) 0.84 (t, *J*=7.53 Hz, 3 H). MS: MS *m/z* 858.2 (M^++1).

Preparation of Compound 4377

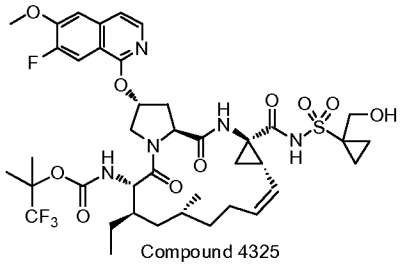


Compound 4377

Compound 4377 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4377: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,6-dimethoxyquinolin-3-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 9.07 (s, 1 H) 8.70 (d, *J*=2.51 Hz, 1 H) 8.02 - 8.07 (m, 1 H) 7.52 (s, 1 H) 7.35 (d, *J*=2.51 Hz, 1 H) 7.07 (dd, *J*=9.04, 2.51 Hz, 1 H) 6.52 (d, *J*=3.01 Hz, 1 H) 5.61 - 5.68 (m, 1 H) 5.00 (s, 1 H) 4.66 (dd, *J*=10.29, 6.78 Hz, 1 H) 4.06 - 4.14 (m, 1 H) 4.50 - 4.65 (m, 3 H) 3.98 - 4.05 (m, 3 H) 3.98 (br. s., 2 H) 3.12 - 3.18 (m, 1 H) 2.85 (dd, *J*=13.80, 6.78 Hz, 1 H) 2.70 - 2.76 (m, 1 H) 2.50 - 2.58 (m, 1 H) 2.36 - 2.50 (m, 2 H) 1.97 (d, *J*=13.55 Hz, 2 H) 1.77 (dd, *J*=8.53, 5.52 Hz, 1 H) 1.62 - 1.70 (m, 1 H) 1.57 (dd, *J*=10.29, 4.77 Hz, 7 H) 1.44 (dd, *J*=9.79, 4.27 Hz, 2 H) 1.31 (s, 1 H) 1.07 - 1.18 (m, 9 H) 1.02 (d, *J*=6.53 Hz, 3 H) 0.81 - 0.94 (m, 5 H). MS: MS *m/z* 812.5 (M^++1).

Preparation of Compound 4325

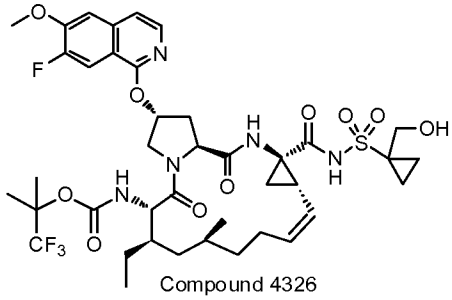


Compound 4325

Compound 4325 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3, using tert-butyl ((2S,3R)-3-ethyl-1-((2S,4R)-4-hydroxy-2-(((1R,2S)-1-(((1-(hydroxymethyl)cyclopropyl)sulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)pyrrolidin-1-yl)-5-methyl-1-oxonon-8-en-2-yl)carbamate as a reagent.

Compound 4325: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(hydroxymethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.97 (d, *J*=6.02 Hz, 1 H) 7.79 (d, *J*=12.05 Hz, 1 H) 7.40 (d, *J*=8.53 Hz, 1 H) 7.31 (d, *J*=5.52 Hz, 1 H) 5.89 (br. s., 1 H) 5.53 - 5.66 (m, 1 H) 5.39 (s, 1 H) 4.68 - 4.76 (m, 1 H) 4.50 - 4.64 (m, 2 H) 4.41 (s, 1 H) 3.96 - 4.12 (m, 5 H) 2.67 - 2.76 (m, 1 H) 2.58 - 2.65 (m, 1 H) 2.40 - 2.54 (m, 1 H) 1.87 - 2.00 (m, 2 H) 1.65 - 1.75 (m, 2 H) 1.37 - 1.46 (m, 7 H) 1.26 - 1.34 (m, 2 H) 1.16 - 1.22 (m, 4 H) 1.12 (s, 3 H) 0.98 - 1.10 (m, 5 H) 0.84 (t, *J*=7.53 Hz, 3 H). MS: MS *m/z* 870.4 (M^++1).

Preparation of Compound 4326

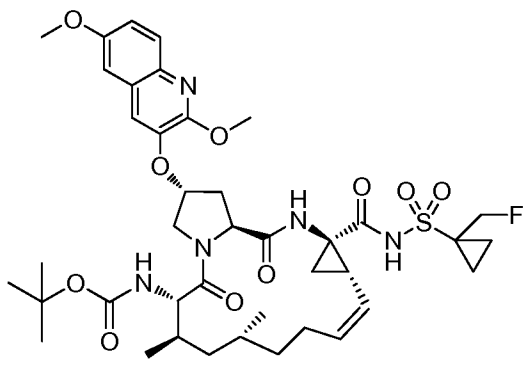


Compound 4326

Compound 4326 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3, using tert-butyl ((2S,3R)-3-ethyl-1-((2S,4R)-4-hydroxy-2-(((1R,2S)-1-(((1-(hydroxymethyl)cyclopropyl)sulfonyl)carbamoyl)-2-vinylcyclopropyl)carbamoyl)pyrrolidin-1-yl)-5-methyl-1-oxonon-8-en-2-yl)carbamate as a reagent.

Compound 4326: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(hydroxymethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 7.96 (d, J=6.02 Hz, 1 H) 7.85 (d, J=11.55 Hz, 1 H) 7.40 (d, J=8.53 Hz, 1 H) 7.31 (d, J=5.52 Hz, 1 H) 5.88 (br. s., 1 H) 5.67 - 5.75 (m, 1 H) 5.36 (t, J=9.79 Hz, 1 H) 4.73 (t, J=8.28 Hz, 1 H) 4.48 - 4.55 (m, 2 H) 4.34 - 4.43 (m, 2 H) 4.01 - 4.07 (m, 4 H) 2.65 - 2.72 (m, 1 H) 2.48 - 2.58 (m, 1 H) 2.36 (d, J=9.54 Hz, 1 H) 2.02 (s, 1 H) 1.81 (br. s., 1 H) 1.57 - 1.71 (m, 4 H) 1.51 (s, 4 H) 1.42 - 1.46 (m, 1 H) 1.26 - 1.35 (m, 8 H) 1.13 - 1.21 (m, 1 H) 0.98 - 1.09 (m, 4 H) 0.90 (d, J=6.53 Hz, 3 H). MS: MS m/z 870.4 (M^++1).

Preparation of Compound 4376



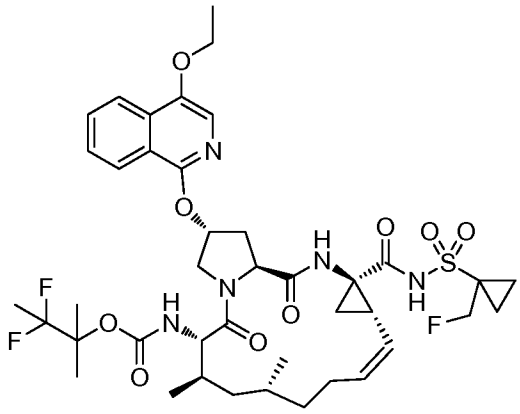
Compound 4376

Compound 4376 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of 4001.

Compound 4376 : tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,6-dimethoxyquinolin-3-yl)oxy)-14a-(((1-

(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.66 (d, *J*=9.04 Hz, 1 H) 7.56 (s, 1 H) 7.12 - 7.20 (m, 2 H) 6.68 (d, *J*=9.04 Hz, 1 H) 5.59 - 5.66 (m, 1 H) 5.27 - 5.32 (m, 1 H) 4.96 - 5.04 (m, 1 H) 4.50 - 4.65 (m, 3 H) 3.98 - 4.05 (m, 3 H) 3.94 (s, 4 H) 2.63 - 2.77 (m, 2 H) 2.38 - 2.46 (m, 2 H) 1.99 (br. s., 1 H) 1.87 (br. s., 1 H) 1.65 - 1.80 (m, 3 H) 1.59 (dd, *J*=9.29, 5.27 Hz, 1 H) 1.50 (d, *J*=8.03 Hz, 2 H) 1.16 - 1.28 (m, 11 H) 0.95 - 1.04 (m, 5 H) 0.82 (t, *J*=11.29 Hz, 1 H). MS: MS *m/z* 816.4 (M^++1).

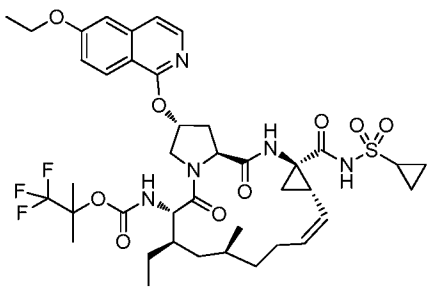
Preparation of Compound 5355



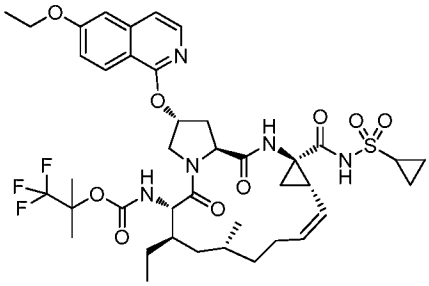
Compound 5355

Compound 5355 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117: Compound 5355: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 850.6 (M^++1).

Preparation of Compound 5356 and Compound 5357



Compound 5356



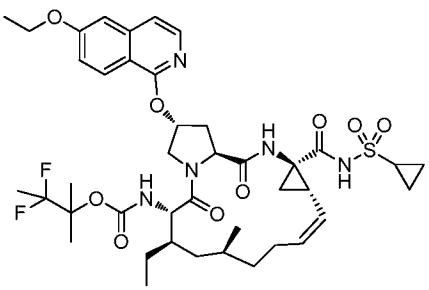
Compound 5357

Compounds 5356 and 5357 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

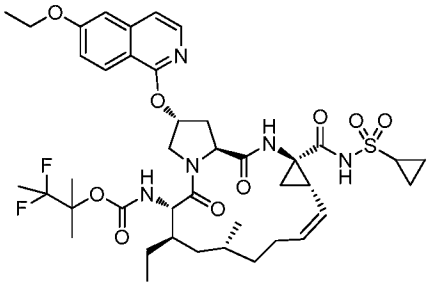
Compound 5356: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 836.5 (M^++1).

Compound 5357: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (br. s., 1H), 9.00 (br. s., 1H), 8.03 - 7.93 (m, 2H), 7.86 (d, *J*=8.5 Hz, 1H), 7.35 - 7.27 (m, 2H), 7.14 (dd, *J*=9.2, 2.4 Hz, 1H), 5.82 (br. s., 1H), 5.53 (br. s., 1H), 5.06 (br. s., 1H), 4.57 - 4.43 (m, 2H), 4.18 (q, *J*=7.0 Hz, 2H), 3.96 - 3.86 (m, 2H), 2.91 (d, *J*=6.1 Hz, 1H), 2.73 - 2.58 (m, 2H), 2.40 - 2.25 (m, 2H), 2.01 - 1.86 (m, 2H), 1.65 - 1.30 (m, 14H), 1.23 - 0.88 (m, 12H), 0.73 (t, *J*=7.5 Hz, 3H). MS: MS m/z 836.5 (M^++1).

Preparation of Compound 5358 and Compound 5359



Compound 5358



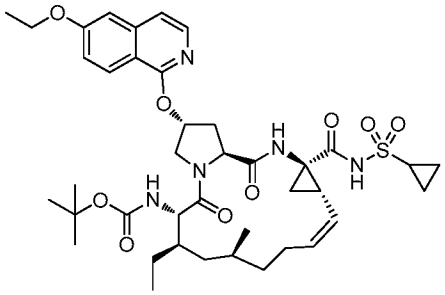
Compound 5359

Compounds 5358 and 5359 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

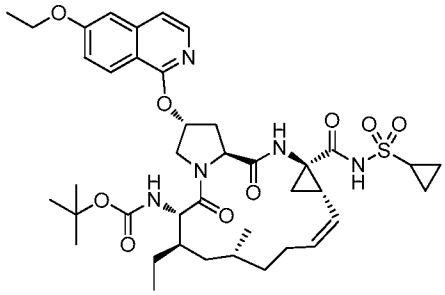
Compound 5358: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 832.7 (M^++1).

Compound 5359: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.98 (s, 1H), 8.02 - 7.93 (m, 2H), 7.66 (d, *J*=8.5 Hz, 1H), 7.33 - 7.27 (m, 2H), 7.13 (dd, *J*=9.2, 2.4 Hz, 1H), 5.82 (br. s., 1H), 5.60 - 5.47 (m, 1H), 5.06 (t, *J*=10.1 Hz, 1H), 4.57 - 4.43 (m, 2H), 4.18 (q, *J*=7.0 Hz, 2H), 3.96 - 3.86 (m, 2H), 2.96 - 2.88 (m, 1H), 2.76 - 2.60 (m, 2H), 2.39 - 2.25 (m, 2H), 1.93 (d, *J*=10.7 Hz, 2H), 1.65 - 0.92 (m, 28H), 0.75 (t, *J*=7.5 Hz, 3H). MS: MS m/z 832.7 (M^++1).

Preparation of Compound 5360 and Compound 5361



Compound 5360



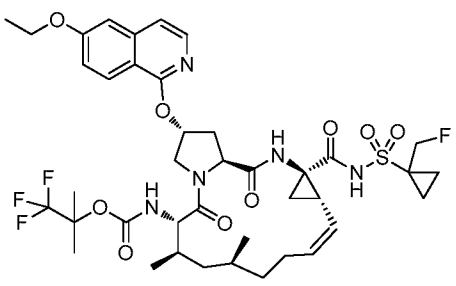
Compound 5361

Compounds 5360 and 5361 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

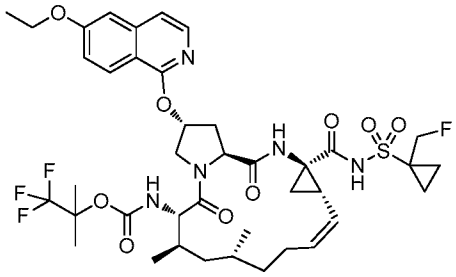
Compound 5360: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 782.5 (M^++1).

Compound 5361: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.96 (s, 1H), 8.02 (d, *J*=9.2 Hz, 1H), 7.95 (d, *J*=6.1 Hz, 1H), 7.31 - 7.27 (m, 2H), 7.20 (d, *J*=8.9 Hz, 1H), 7.10 (dd, *J*=9.0, 2.3 Hz, 1H), 5.81 (br. s., 1H), 5.53 (d, *J*=6.1 Hz, 1H), 5.05 (t, *J*=9.8 Hz, 1H), 4.60 (d, *J*=10.7 Hz, 1H), 4.47 - 4.40 (m, 1H), 4.18 (q, *J*=7.0 Hz, 2H), 3.98 - 3.87 (m, 2H), 2.91 (br. s., 1H), 2.76 - 2.58 (m, 2H), 2.40 - 2.23 (m, 2H), 2.01 - 1.87 (m, 2H), 1.63 - 0.88 (m, 28H), 0.74 (t, *J*=7.3 Hz, 3H). MS: MS m/z 782.6 (M^++1).

Preparation of Compound 5362 and Compound 5363



Compound 5362



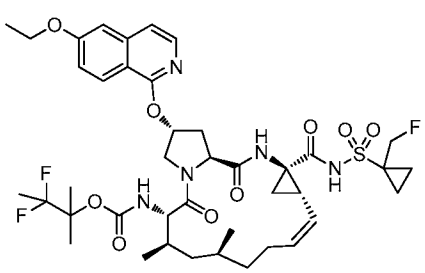
Compound 5363

Compounds 5362 and 5363 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

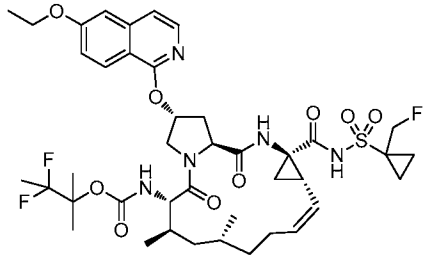
Compound 5362: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 854.5 (M^++1).

Compound 5363: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (s, 1H), 9.05 (s, 1H), 8.06 - 7.92 (m, 2H), 7.84 (d, *J*=7.9 Hz, 1H), 7.37 - 7.25 (m, 2H), 7.14 (dd, *J*=9.2, 2.4 Hz, 1H), 5.81 (br. s., 1H), 5.60 - 5.45 (m, 1H), 4.99 (t, *J*=9.8 Hz, 1H), 4.89 - 4.73 (m, 1H), 4.62 - 4.45 (m, 3H), 4.18 (q, *J*=7.0 Hz, 2H), 3.96 - 3.86 (m, 1H), 3.72 (dd, *J*=10.5, 8.1 Hz, 1H), 2.72 - 2.57 (m, 2H), 2.38 - 2.21 (m, 2H), 1.95 - 1.79 (m, 2H), 1.70 (dd, *J*=13.1, 6.7 Hz, 1H), 1.59 - 1.09 (m, 18H), 0.96 - 0.86 (m, 6H), 0.75 (t, *J*=12.2 Hz, 1H). MS: MS m/z 854.5 (M^++1).

Preparation of Compound 5364 and Compound 5365



Compound 5364



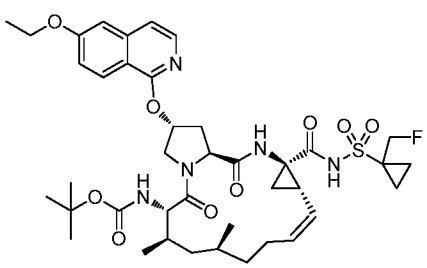
Compound 5365

Compounds 5364 and 5365 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

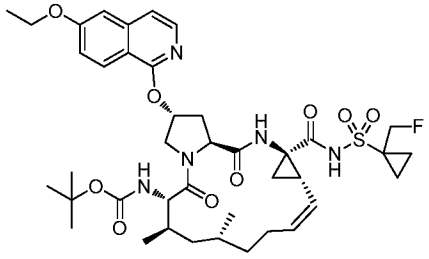
Compound 5364: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 850.5 (M^++1).

Compound 5365: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.03 (s, 1H), 8.01 (d, *J*=9.2 Hz, 1H), 7.96 (d, *J*=5.8 Hz, 1H), 7.63 (d, *J*=8.2 Hz, 1H), 7.33 - 7.27 (m, 2H), 7.12 (dd, *J*=9.2, 2.4 Hz, 1H), 5.82 (br. s., 1H), 5.58 - 5.47 (m, 1H), 5.00 (t, *J*=9.9 Hz, 1H), 4.88 - 4.74 (m, 1H), 4.62 - 4.44 (m, 3H), 4.18 (q, *J*=6.9 Hz, 2H), 3.95 - 3.89 (m, 2H), 3.73 (dd, *J*=10.5, 8.4 Hz, 1H), 2.73 - 2.57 (m, 2H), 2.39 - 2.24 (m, 2H), 1.95 - 1.79 (m, 2H), 1.73 - 1.04 (m, 21H), 0.92 (dd, *J*=19.5, 6.7 Hz, 6H), 0.76 (t, *J*=12.2 Hz, 1H). MS: MS m/z 850.7 (M^++1).

Preparation of Compound 5366 and Compound 5367



Compound 5366



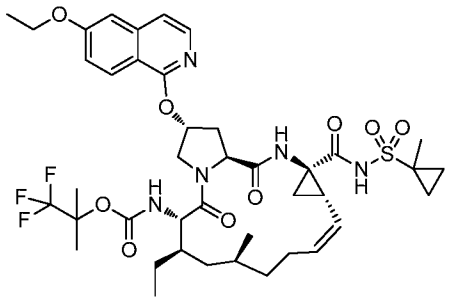
Compound 5367

Compounds 5366 and 5367 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

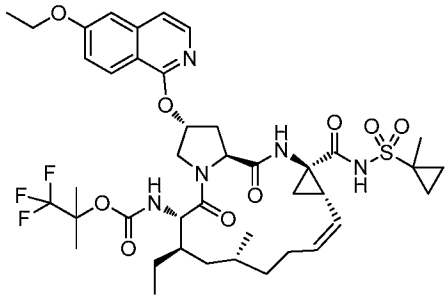
Compound 5366: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 800.5 (M^++1).

Compound 5367: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 800.5 (M^++1).

Preparation of Compound 5368 and Compound 5369



Compound 5368



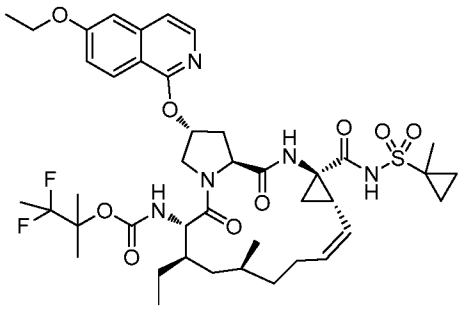
Compound 5369

Compounds 5368 and 5369 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

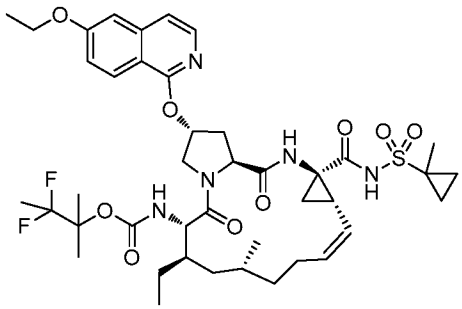
Compound 5368: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 850.5 (M^++1).

Compound 5369: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.13 (br. s., 1H), 8.04 - 7.94 (m, 2H), 7.87 (d, *J*=8.5 Hz, 1H), 7.35 - 7.28 (m, 2H), 7.14 (dd, *J*=9.2, 2.4 Hz, 1H), 5.84 (br. s., 1H), 5.54 (br. s., 1H), 4.98 (br. s., 1H), 4.53 (t, *J*=11.9 Hz, 2H), 4.18 (q, *J*=7.0 Hz, 2H), 3.99 - 3.87 (m, 2H), 2.76 - 2.56 (m, 2H), 2.40 - 2.26 (m, 2H), 2.02 - 1.85 (m, 2H), 1.67 - 0.85 (m, 28H), 0.74 (t, *J*=7.5 Hz, 3H). MS: MS m/z 850.5 (M^++1).

Preparation of Compound 5370 and Compound 5371



Compound 5370



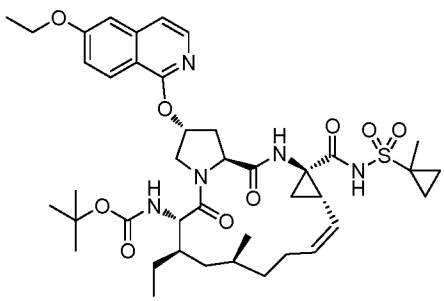
Compound 5371

Compounds 5370 and 5371 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

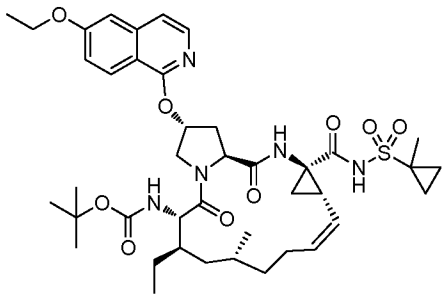
Compound 5370: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 846.5 (M^++1).

Compound 5371: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 846.5 (M^++1).

Preparation of Compound 5372 and Compound 5373



Compound 5372



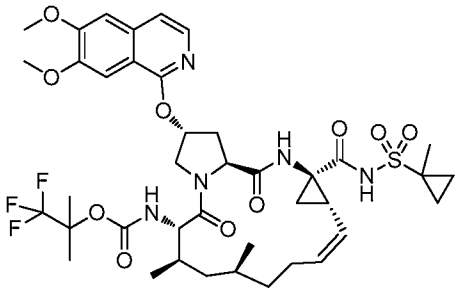
Compound 5373

Compounds 5372 and 5373 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

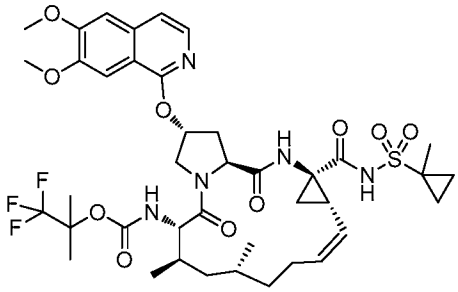
Compound 5372: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 796.5 (M^++1).

Compound 5373: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 796.5 (M^++1).

Preparation of Compound 5374 and Compound 5375



Compound 5374



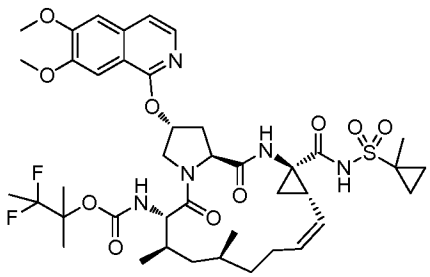
Compound 5375

Compounds 5374 and 5375 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

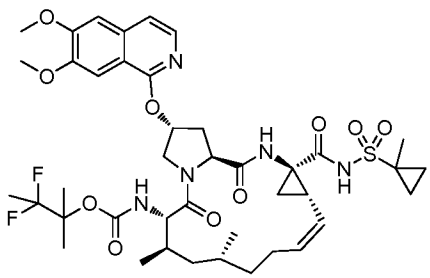
Compound 5374: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 852.8 (M^++1).

Compound 5375: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.17 (s, 1H), 7.89 (d, *J*=5.8 Hz, 1H), 7.79 (d, *J*=8.2 Hz, 1H), 7.33 (d, *J*=5.8 Hz, 2H), 7.28 (d, *J*=5.8 Hz, 1H), 5.83 (br. s., 1H), 5.59 - 5.49 (m, 1H), 4.98 (t, *J*=9.8 Hz, 1H), 4.55 (dd, *J*=9.9, 7.2 Hz, 1H), 4.47 (d, *J*=11.9 Hz, 1H), 3.98 (dd, *J*=11.4, 3.5 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.71 (dd, *J*=10.8, 8.4 Hz, 1H), 2.76 - 2.60 (m, 2H), 2.40 - 2.28 (m, 2H), 1.95 - 1.80 (m, 2H), 1.73 - 1.59 (m, 2H), 1.58 - 1.50 (m, 1H), 1.48 - 1.08 (m, 12H), 0.97 - 0.84 (m, 10H), 0.75 (t, *J*=12.5 Hz, 1H). MS: MS m/z 852.8 (M^++1).

Preparation of Compound 5376 and Compound 5377



Compound 5376



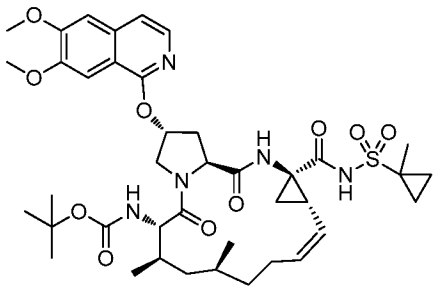
Compound 5377

Compounds 5376 and 5377 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

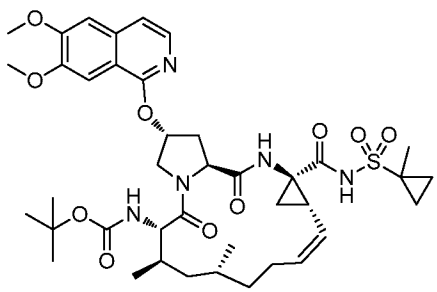
Compound 5376: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 848.8 (M^++1).

Compound 5377: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 848.8 (M^++1).

Preparation of Compound 5378 and Compound 5379



Compound 5378



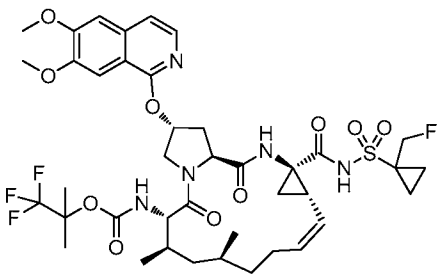
Compound 5379

Compounds 5378 and 5379 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

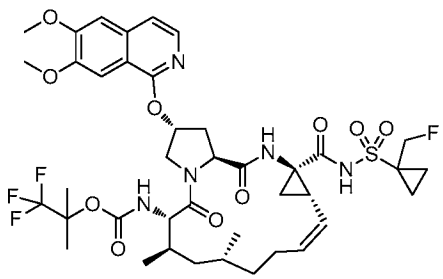
Compound 5378: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 798.5 (M^++1).

Compound 5379: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 798.5 (M^++1).

Preparation of Compound 5380 and Compound 5381



Compound 5380



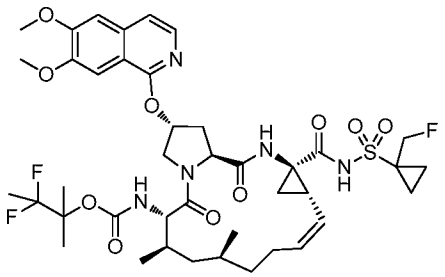
Compound 5381

Compounds 5380 and 5381 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

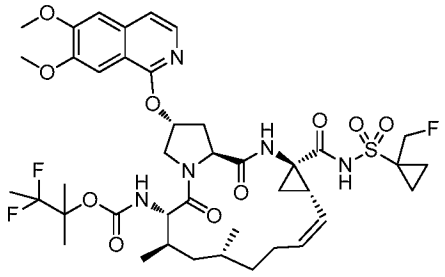
Compound 5380: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 870.5 (M^++1).

Compound 5381: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 870.5 (M^++1).

Preparation of Compound 5382 and Compound 5383



Compound 5382



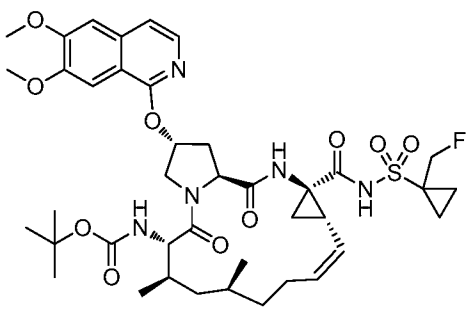
Compound 5383

Compounds 5382 and 5383 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

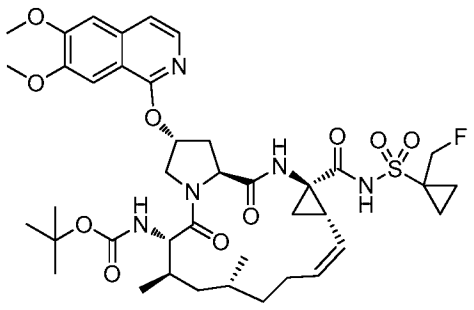
Compound 5382: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate MS: MS m/z 866.8 (M^++1).

Compound 5383: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 866.9 (M^++1).

Preparation of Compound 5384 and Compound 5385



Compound 5384



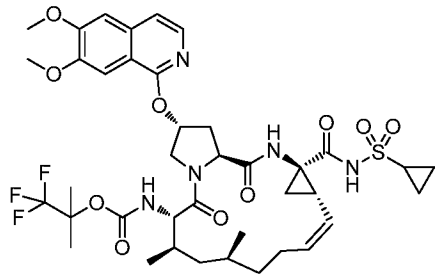
Compound 5385

Compounds 5384 and 5385 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

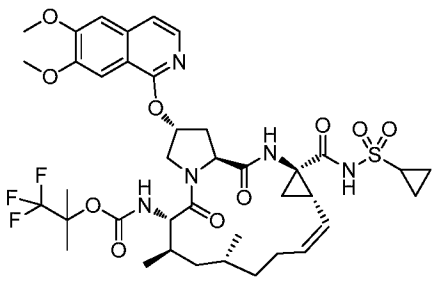
Compound 5384: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 816.5 (M^++1).

Compound 5385: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 816.5 (M^++1).

Preparation of Compound 5386 and Compound 5387



Compound 5386



Compound 5387

Compounds 5386 and 5387 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

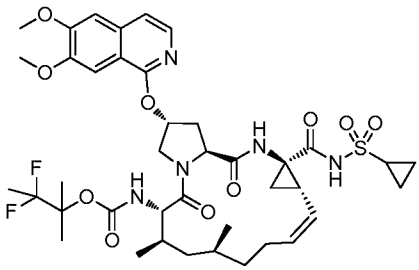
Compound 5386: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 838.5 (M^++1).

Compound 5387: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.21 (s, 1H), 9.04 (s, 1H), 7.89 (d, *J*=5.5 Hz, 1H), 7.79 (d, *J*=8.2 Hz, 1H), 7.33 (d, *J*=6.1 Hz, 2H), 7.28 (d, *J*=5.8 Hz, 1H), 5.81 (br. s., 1H), 5.57 - 5.49 (m, 1H), 5.06 (t, *J*=9.9

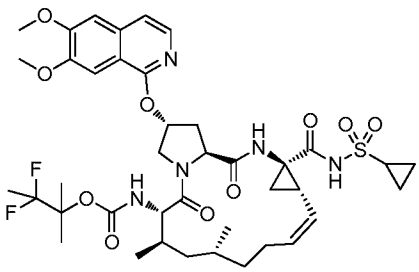
Hz, 1H), 4.55 - 4.43 (m, 2H), 3.99 - 3.90 (m, 5H), 3.87 (s, 3H), 3.71 (dd, *J*=10.4, 8.5 Hz, 1H), 2.96 - 2.89 (m, 1H), 2.73 - 2.59 (m, 2H), 2.39 - 2.25 (m, 2H), 1.96 - 1.80 (m, 2H), 1.70 (dd, *J*=12.8, 6.4 Hz, 1H), 1.64 - 1.55 (m, 2H), 1.48 - 1.33 (m, 2H), 1.30 (s, 3H), 1.19 - 1.06 (m, 3H), 1.06 - 0.91 (m, 7H), 0.87 (d, *J*=6.4 Hz, 3H), 0.74 (t, *J*=12.5 Hz, 1H).

MS: MS m/z 838.5 (M^++1).

Preparation of Compound 5388 and Compound 5389



Compound 5388



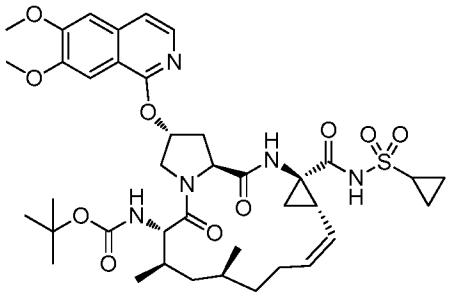
Compound 5389

Compounds 5388 and 5389 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

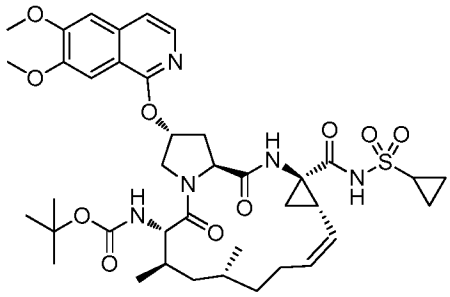
Compound 5388: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 834.8 (M^++1).

Compound 5389: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 834.8 (M^++1).

Preparation of Compound 5390 and Compound 5391



Compound 5390



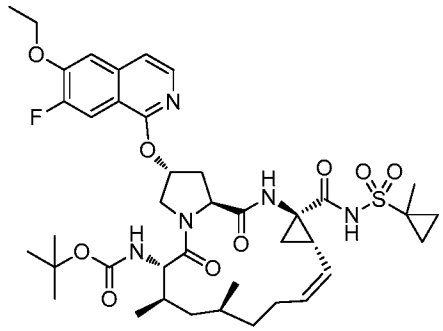
Compound 5391

Compounds 5390 and 5391 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

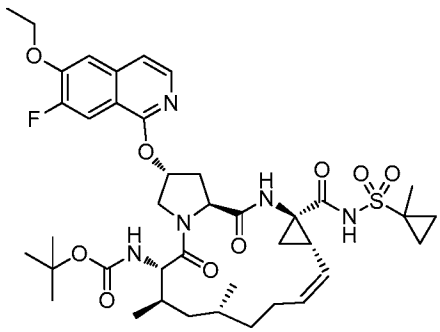
Compound 5390: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 784.5 (M^++1).

Compound 5391: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 784.5 (M^++1).

Preparation of Compound 5392 and Compound 5393



Compound 5392



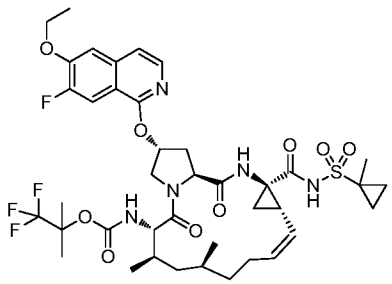
Compound 5393

Compounds 5392 and 5393 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

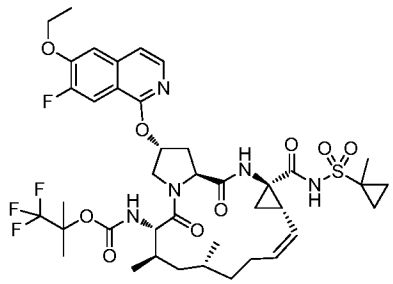
Compound 5392: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 800.5 (M^++1).

Compound 5393: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.08 (s, 1H), 7.98 (d, *J*=5.8 Hz, 1H), 7.72 (d, *J*=11.6 Hz, 1H), 7.54 (d, *J*=8.2 Hz, 1H), 7.34 (d, *J*=5.8 Hz, 1H), 7.21 (d, *J*=7.9 Hz, 1H), 5.81 (br. s., 1H), 5.60 - 5.47 (m, 1H), 4.98 (t, *J*=10.1 Hz, 1H), 4.59 (d, *J*=11.3 Hz, 1H), 4.49 (dd, *J*=10.2, 6.9 Hz, 1H), 4.26 (q, *J*=7.0 Hz, 2H), 3.94 - 3.87 (m, 1H), 3.69 (dd, *J*=10.7, 7.9 Hz, 1H), 2.77 - 2.57 (m, 2H), 2.39 - 2.25 (m, 2H), 1.94 - 1.76 (m, 2H), 1.74 - 1.65 (m, 1H), 1.64 - 1.58 (m, 1H), 1.52 (dd, *J*=9.2, 4.9 Hz, 1H), 1.48 - 1.26 (m, 10H), 1.19 - 1.07 (m, 10H), 0.91 (dd, *J*=18.3, 6.4 Hz, 8H), 0.74 (t, *J*=12.5 Hz, 1H). MS: MS m/z 800.9 (M^++1).

Preparation of Compound 5394 and Compound 5395



Compound 5394



Compound 5395

Compounds 5394 and 5395 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

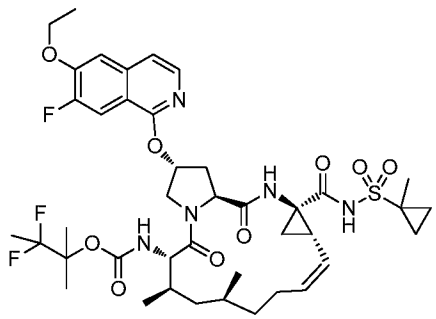
Compound 5394: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 854.8 (M^++1).

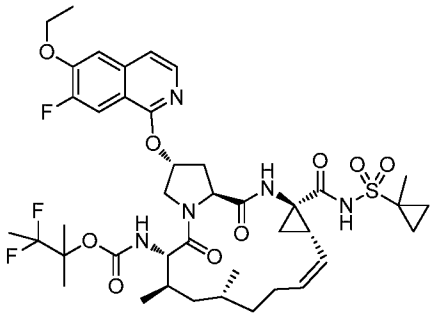
Compound 5395: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (s, 1H), 9.11 (s, 1H), 7.98 (d, *J*=5.8 Hz, 1H), 7.87 (d, *J*=7.6 Hz, 1H), 7.73 (d, *J*=11.3 Hz, 1H), 7.56 (d, *J*=8.5 Hz, 1H), 7.35 (d, *J*=6.1 Hz, 1H), 5.81 (br. s., 1H), 5.61 - 5.46 (m, 1H), 4.98 (t, *J*=9.9 Hz, 1H), 4.58 - 4.45 (m, 2H), 4.27 (q, *J*=7.0 Hz, 2H), 3.96 - 3.85 (m, 1H), 3.71 (dd, *J*=10.7, 7.6 Hz, 1H), 2.76 - 2.58 (m, 2H), 2.40 - 2.26 (m, 2H), 1.95 - 1.79 (m, 2H), 1.72 (dd, *J*=12.7, 6.9 Hz, 1H), 1.64 - 1.58 (m, 1H), 1.53 (dd, *J*=9.3, 5.3 Hz, 1H), 1.48 - 1.07 (m, 16H), 0.92 (dd, *J*=13.4, 6.7 Hz, 9H), 0.77 (t, *J*=12.4 Hz, 1H).

MS: MS m/z 854.8 (M^++1).

Preparation of Compound 5396 and Compound 5397



Compound 5396



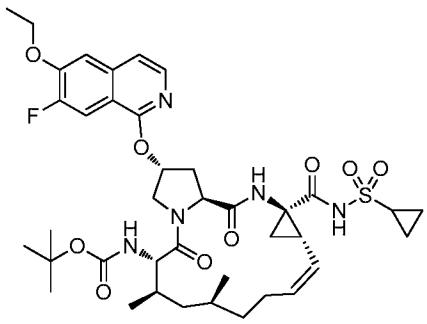
Compound 5397

Compounds 5396 and 5397 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

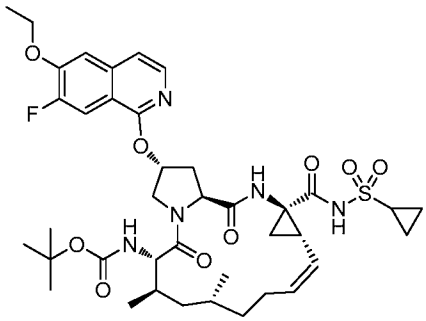
Compound 5396: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 850.8 (M^++1).

Compound 5397: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 850.9 (M^++1).

Preparation of Compound 5398 and Compound 5399



Compound 5398



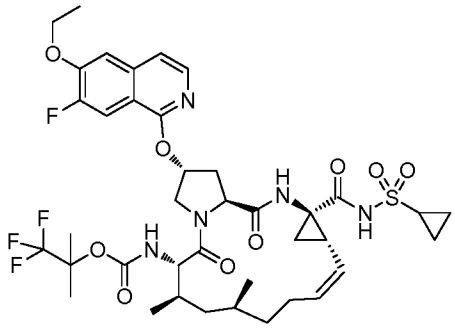
Compound 5399

Compounds 5398 and 5399 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

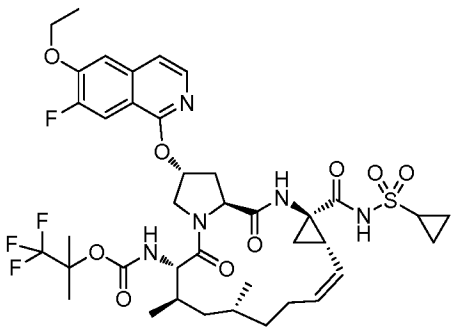
Compound 5398: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 850.8 (M^++1).

Compound 5399: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 850.9 (M^++1).

Preparation of Compound 5400 and Compound 5401



Compound 5400



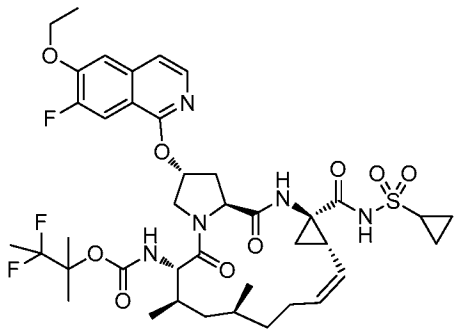
Compound 5401

Compounds 5400 and 5401 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

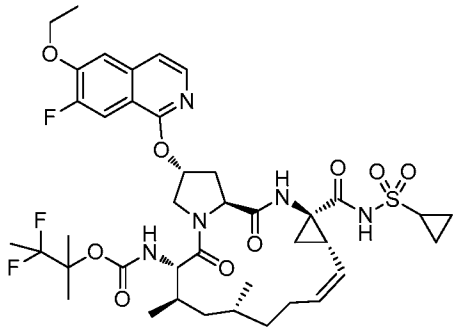
Compound 5400: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 840.4 (M^++1).

Compound 5401: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.17 (s, 1H), 8.97 (s, 1H), 7.98 (d, *J*=5.8 Hz, 1H), 7.86 (d, *J*=7.6 Hz, 1H), 7.73 (d, *J*=11.3 Hz, 1H), 7.56 (d, *J*=8.5 Hz, 1H), 7.35 (d, *J*=6.1 Hz, 1H), 5.79 (br. s., 1H), 5.53 (d, *J*=6.4 Hz, 1H), 5.06 (t, *J*=9.8 Hz, 1H), 4.56 - 4.44 (m, 2H), 4.27 (q, *J*=7.0 Hz, 2H), 3.94 - 3.85 (m, 1H), 3.71 (dd, *J*=10.7, 7.6 Hz, 1H), 2.91 (d, *J*=5.8 Hz, 1H), 2.72 - 2.59 (m, 2H), 2.39 - 2.25 (m, 2H), 1.94 - 1.80 (m, 2H), 1.77 - 1.68 (m, 1H), 1.65 - 1.51 (m, 2H), 1.49 - 0.85 (m, 22H), 0.75 (t, *J*=12.7 Hz, 1H). MS: MS m/z 840.8 (M^++1).

Preparation of Compound 5402 and Compound 5403



Compound 5402



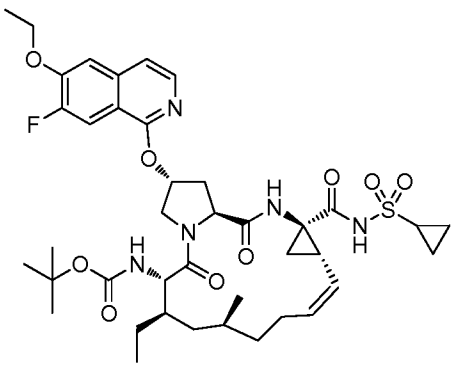
Compound 5403

Compounds 5402 and 5403 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

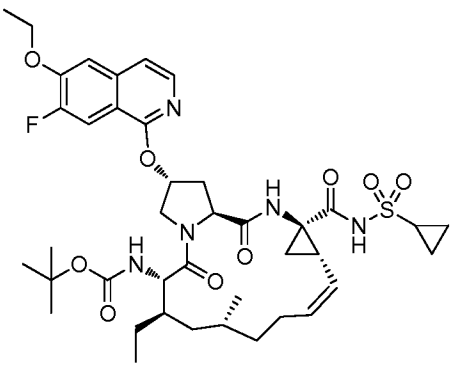
Compound 5402: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 836.5 (M^++1).

Compound 5403: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 836.5 (M^++1).

Preparation of Compound 5404 and Compound 5405



Compound 5404



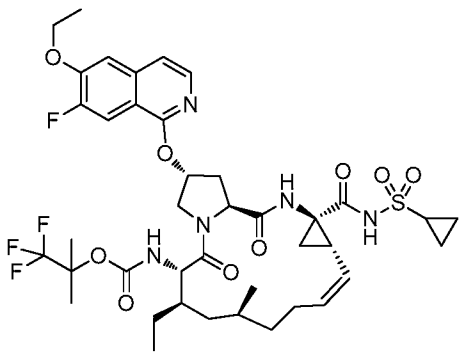
Compound 5405

Compounds 5404 and 5405 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

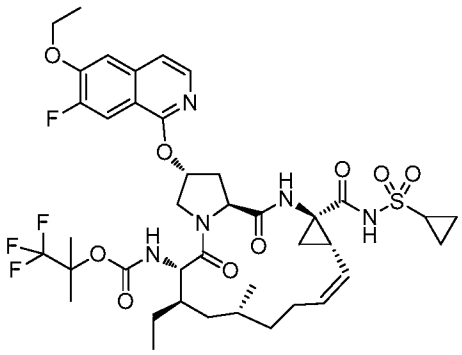
Compound 5404: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 800.6 (M^++1).

Compound 5405: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 800.5 (M^++1).

Preparation of Compound 5406 and Compound 5407



Compound 5406



Compound 5407

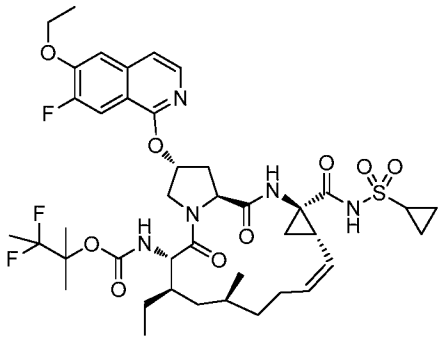
Compounds 5406 and 5407 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5406: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 854.6 (M^++1).

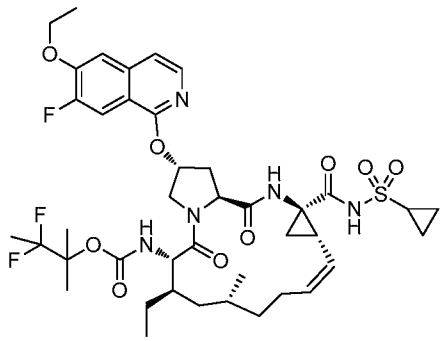
Compound 5407: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.17 (s, 1H), 8.97 (s, 1H), 7.99 (d, *J*=5.8 Hz, 1H), 7.90 (d, *J*=7.9 Hz, 1H), 7.70 (d, *J*=11.6 Hz, 1H), 7.56 (d, *J*=8.5 Hz, 1H), 7.35 (d, *J*=5.8 Hz, 1H), 5.80 (br. s., 1H), 5.59 - 5.42 (m, 1H), 5.07 (t, *J*=9.6 Hz, 1H), 4.60 - 4.43 (m, 2H), 4.27 (q, *J*=7.0 Hz, 2H), 3.98 - 3.84 (m, 2H), 2.97 - 2.86 (m, 1H), 2.73 - 2.60 (m, 2H), 2.38 - 2.24 (m, 2H), 2.01 - 1.83 (m, 2H), 1.71 - 0.89 (m, 25H), 0.74 (t, *J*=7.5 Hz, 3H). MS: MS m/z 854.6 (M^++1).

Preparation of Compound 5408 and Compound 5409



Compound 5408



Compound 5409

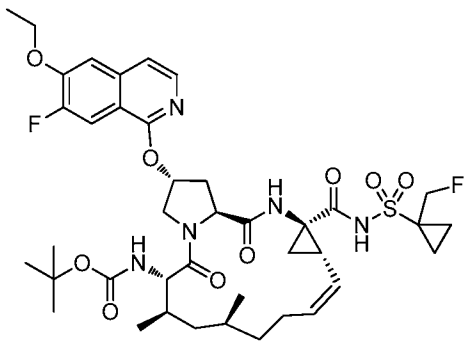
Compounds 5408 and 5409 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5408: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 850.9 (M^++1).

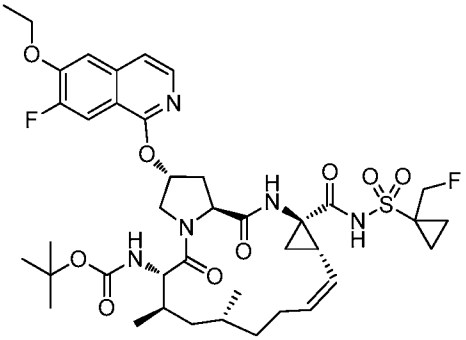
Compound 5409: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.95 (s, 1H), 7.99 (d, *J*=5.8 Hz, 1H), 7.74 - 7.64 (m, 2H), 7.56 (d, *J*=8.2 Hz, 1H), 7.35 (d, *J*=6.1 Hz, 1H), 5.81 (br. s., 1H), 5.65 - 5.49 (m, 1H), 5.07 (t, *J*=9.9 Hz,

1H), 4.61 - 4.44 (m, 2H), 4.27 (q, *J*=6.9 Hz, 2H), 3.99 - 3.83 (m, 2H), 2.97 - 2.87 (m, 1H), 2.79 - 2.59 (m, 2H), 2.39 - 2.25 (m, 2H), 1.93 (d, *J*=7.9 Hz, 2H), 1.69 - 0.89 (m, 28H), 0.75 (t, *J*=7.3 Hz, 3H). MS: MS m/z 850.9 (M^++1).

Preparation of Compound 5410 and Compound 5411



Compound 5410



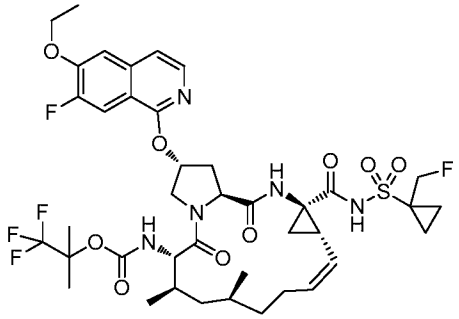
Compound 5411

Compounds 5410 and 5411 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

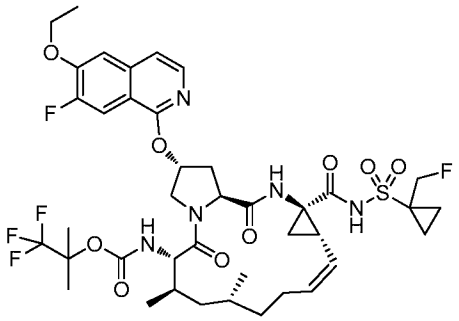
Compound 5410: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 818.6 (M^++1).

Compound 5411: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 818.5 (M^++1).

Preparation of Compound 5412 and Compound 5413



Compound 5412



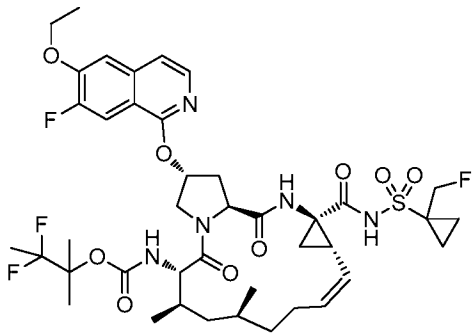
Compound 5413

Compounds 5412 and 5413 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

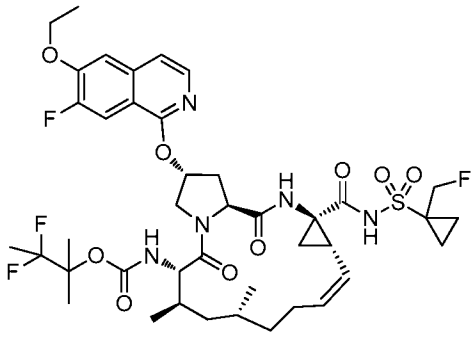
Compound 5412: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 872.5 (M^++1).

Compound 5413: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 872.5 (M^++1).

Preparation of Compound 5414 and Compound 5415



Compound 5414



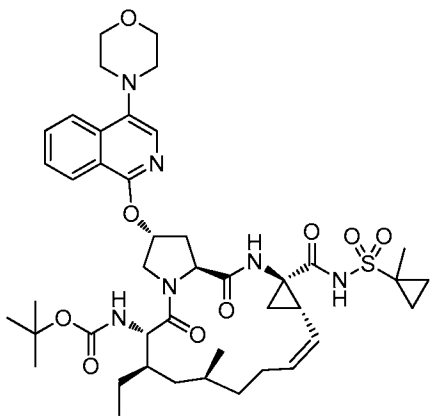
Compound 5415

Compounds 5414 and 5415 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

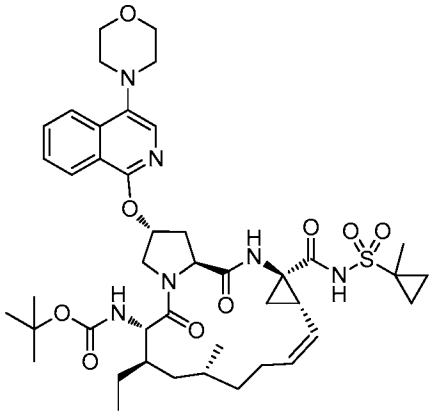
Compound 5414: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 868.5 (M^++1).

Compound 5415: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 885.5 (M^++1).

Preparation of Compound 5416 and Compound 5417



Compound 5416



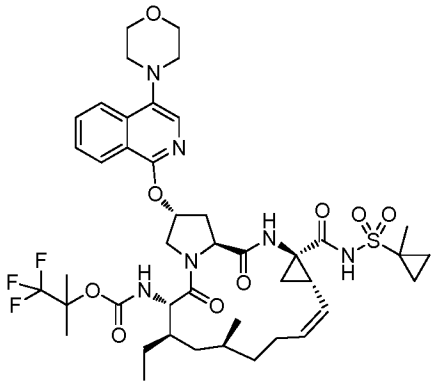
Compound 5417

Compounds 5416 and 5417 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

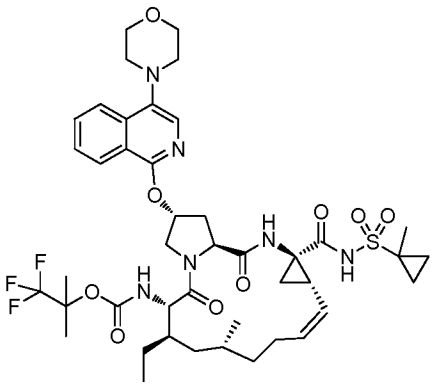
Compound 5416: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 837.6 (M^++1).

Compound 5417: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 837.6 (M^++1).

Preparation of Compound 5418 and Compound 5419



Compound 5418



Compound 5419

Compounds 5418 and 5419 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

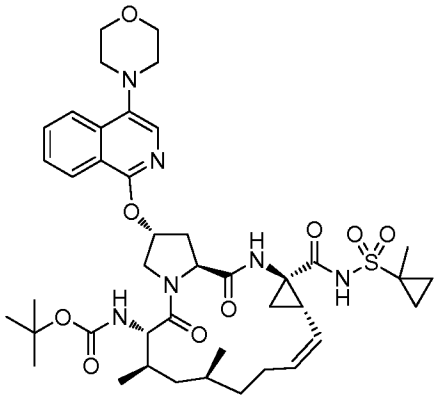
Compound 5418: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 891.6 (M^++1).

Compound 5419: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.13 (s, 1H), 8.10 (dd, *J*=8.2, 4.9 Hz, 2H), 7.91 - 7.74 (m, 3H), 7.60 (t, *J*=7.6 Hz, 1H), 5.81 (br. s., 1H), 5.61 - 5.46 (m, 1H), 4.98 (t, *J*=9.9 Hz, 1H), 4.65 - 4.47 (m, 2H), 4.00 - 3.79 (m, 7H), 3.11 - 2.95 (m,

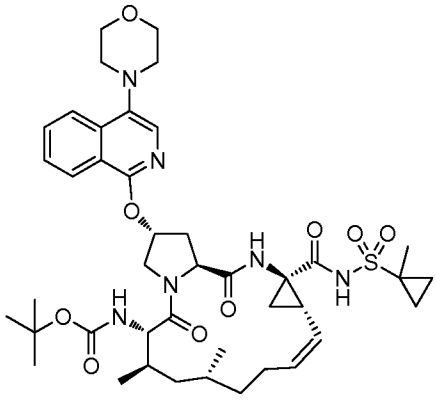
4H), 2.76 - 2.59 (m, 2H), 2.43 - 2.25 (m, 2H), 2.04 - 1.82 (m, 2H), 1.65 - 0.85 (m, 24H), 0.73 (t, *J*=7.5 Hz, 3H).

MS: MS m/z 891.6 (M^++1).

Preparation of Compound 5420 and Compound 5421



Compound 5420



Compound 5421

Compounds 5420 and 5421 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

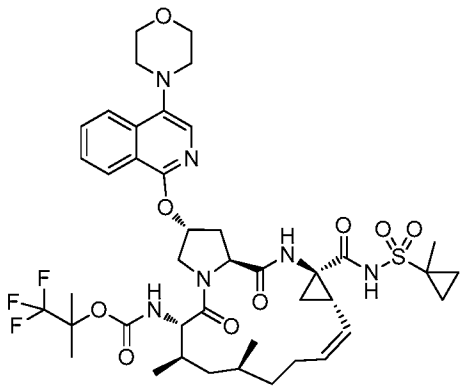
Compound 5420: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate.

MS: MS m/z 823.9 (M^++1).

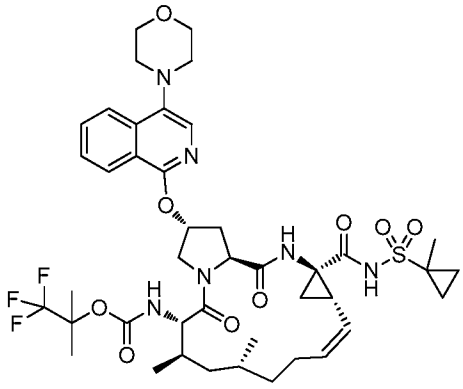
Compound 5421: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate.

MS: MS m/z 824.0 (M^++1).

Preparation of Compound 5422 and Compound 5423



Compound 5422



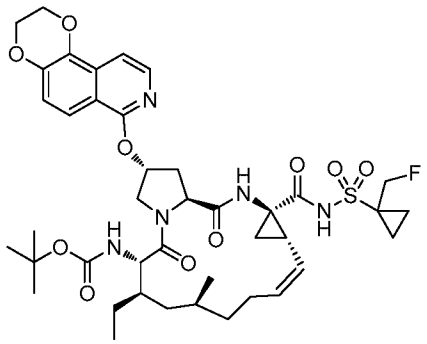
Compound 5423

Compounds 5422 and 5423 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

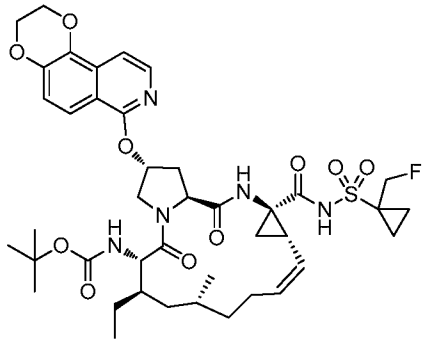
Compound 5422: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 877.6 (M^++1).

Compound 5423: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.14 (br. s., 1H), 8.11 (dd, *J*=14.2, 8.4 Hz, 2H), 7.85 - 7.74 (m, 3H), 7.59 (t, *J*=7.6 Hz, 1H), 5.80 (br. s., 1H), 5.54 (d, *J*=5.5 Hz, 1H), 4.98 (t, *J*=9.9 Hz, 1H), 4.64 - 4.45 (m, 2H), 3.97 - 3.81 (m, 6H), 3.70 (dd, *J*=10.7, 7.9 Hz, 1H), 3.09 - 2.95 (m, 4H), 2.74 - 2.59 (m, 2H), 2.41 - 2.24 (m, 2H), 1.96 - 1.80 (m, 2H), 1.74 - 1.57 (m, 2H), 1.56 - 1.07 (m, 12H), 1.01 - 0.84 (m, 10H), 0.76 (t, *J*=12.7 Hz, 1H). MS: MS m/z 877.6 (M^++1).

Preparation of Compound 5424 and Compound 5425



Compound 5424



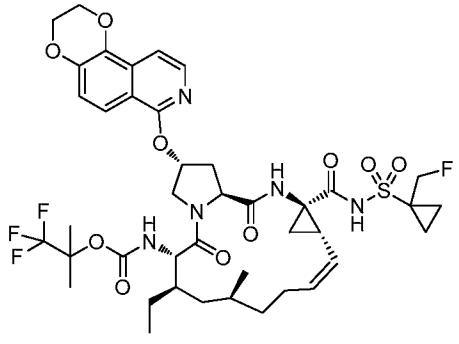
Compound 5425

Compounds 5424 and 5425 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

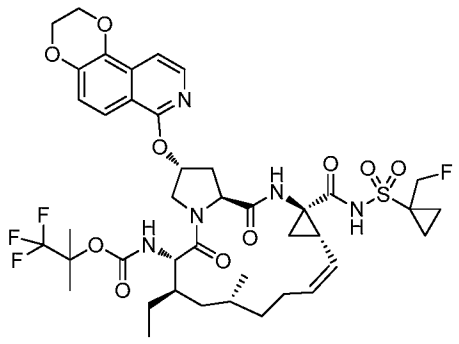
Compound 5424: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 828.6 (M^++1).

Compound 5425: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 828.5 (M^++1).

Preparation of Compound 5426 and Compound 5427



Compound 5426



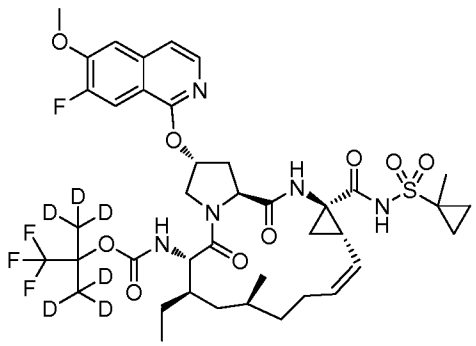
Compound 5427

Compounds 5426 and 5427 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

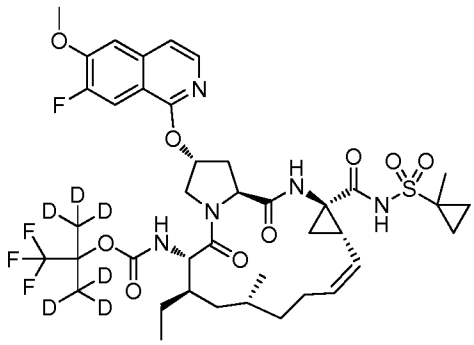
Compound 5426: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 822.5 (M^++1).

Compound 5427: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 822.4 (M^++1).

Preparation of Compound 5428 and Compound 5429



Compound 5428



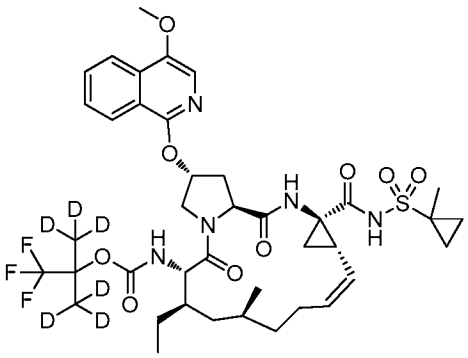
Compound 5429

Compounds 5428 and 5429 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

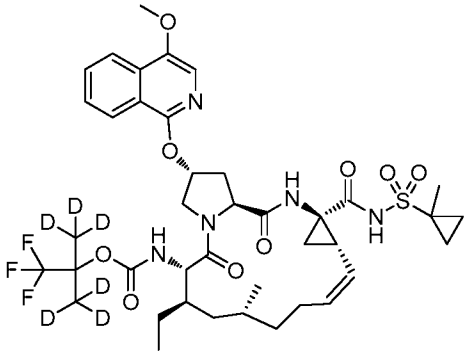
Compound 5428: MS: MS m/z 860.6 (M^++1).

Compound 5429: MS: MS m/z 860.5 (M^++1).

Preparation of Compound 5430 and Compound 5431



Compound 5430



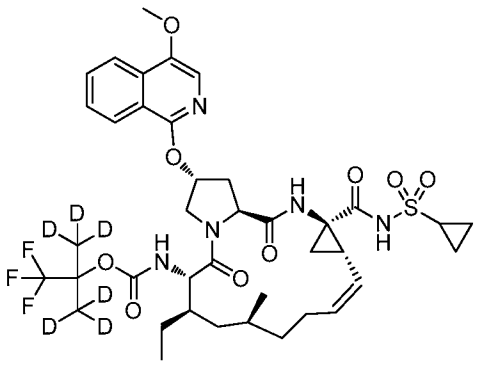
Compound 5431

Compounds 5430 and 5431 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

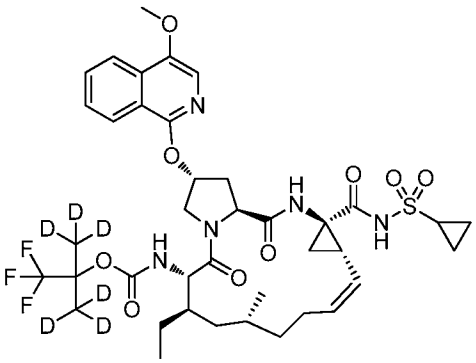
Compound 5430: MS: MS m/z 842.6 (M^++1).

Compound 5431: MS: MS m/z 842.5 (M^++1).

Preparation of Compound 5432 and Compound 5433



Compound 5432



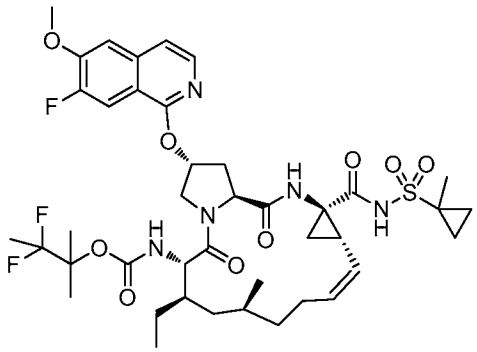
Compound 5433

Compounds 5432 and 5433 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

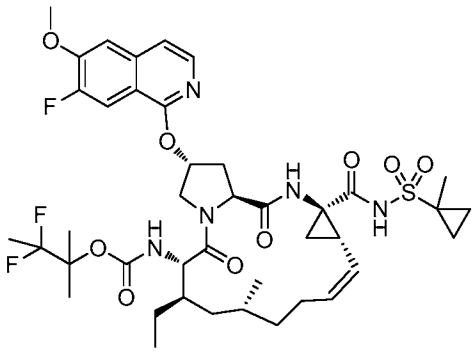
Compound 5432: MS: MS m/z 828.5 (M^++1).

Compound 5433: MS: MS m/z 828.8 (M^++1).

Preparation of Compound 5434 and Compound 5435



Compound 5434



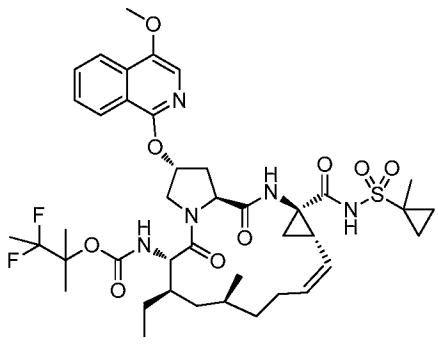
Compound 5435

Compounds 5434 and 5435 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

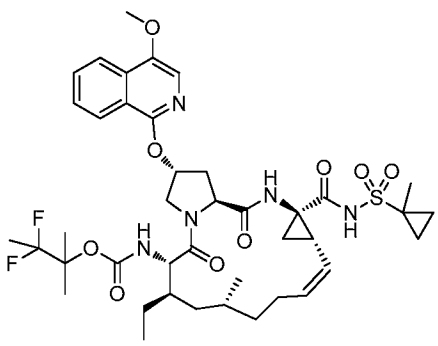
Compound 5434: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 850.9 (M^++1).

Compound 5435: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 850.9 (M^++1).

Preparation of Compound 5436 and Compound 5437



Compound 5436



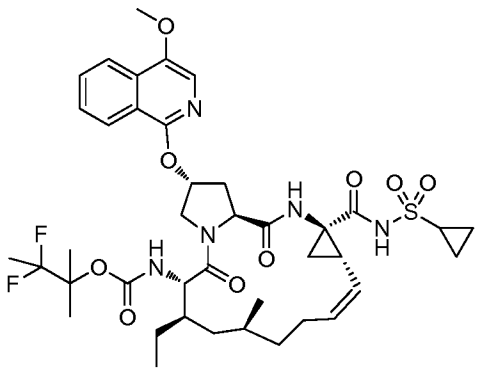
Compound 5437

Compounds 5436 and 5437 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

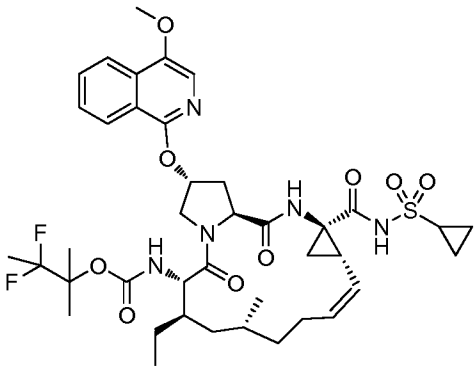
Compound 5436: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 832.9 (M^++1).

Compound 5437: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.11 (s, 1H), 8.07 (dd, *J*=8.2, 3.4 Hz, 2H), 7.83 - 7.77 (m, 1H), 7.68 - 7.59 (m, 3H), 5.79 (br. s., 1H), 5.58 - 5.48 (m, 1H), 4.98 (t, *J*=9.8 Hz, 1H), 4.60 - 4.49 (m, 2H), 4.01 - 3.89 (m, 6H), 2.77 - 2.69 (m, 1H), 2.64 (dd, *J*=13.1, 6.1 Hz, 1H), 2.40 - 2.27 (m, 2H), 1.99 - 1.87 (m, 2H), 1.66 - 0.98 (m, 21H), 0.96 - 0.88 (m, 8H), 0.75 (t, *J*=7.5 Hz, 3H) MS: MS m/z 832.9 (M^++1).

Preparation of Compound 5438 and Compound 5439



Compound 5438



Compound 5439

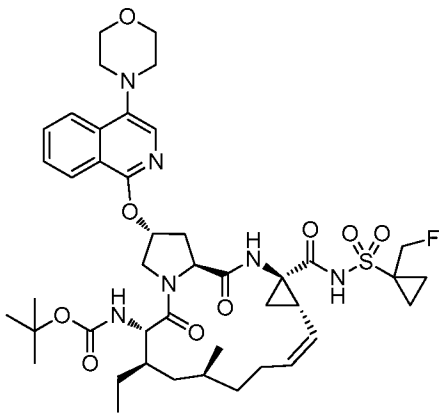
Compounds 5438 and 5439 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5438: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-

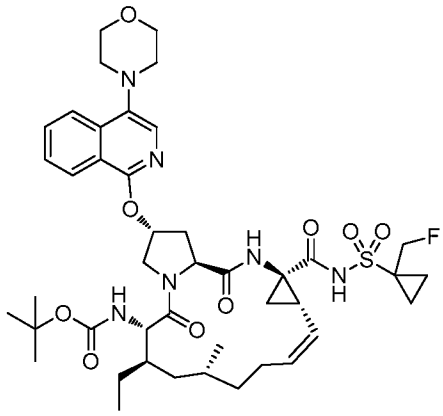
((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 818.6 (M^++1).

Compound 5439: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 818.5 (M^++1).

Preparation of Compound 5440 and Compound 5441



Compound 5440



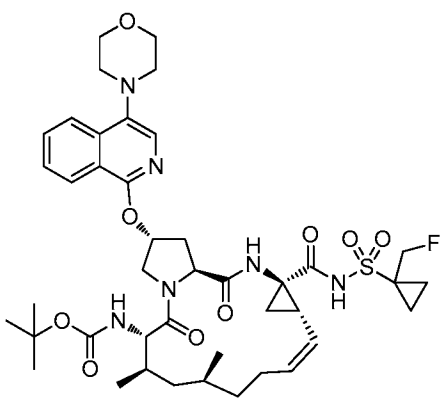
Compound 5441

Compounds 5440 and 5441 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

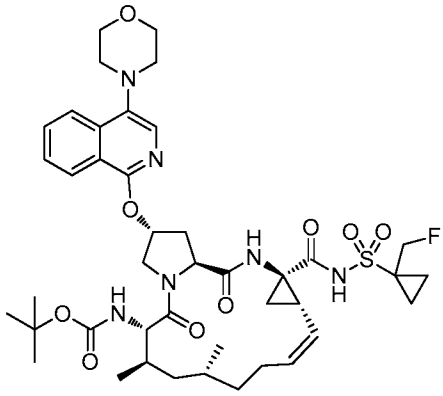
Compound 5440: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 855.6 (M^++1).

Compound 5441: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 855.6 (M^++1).

Preparation of Compound 5442 and Compound 5443



Compound 5442



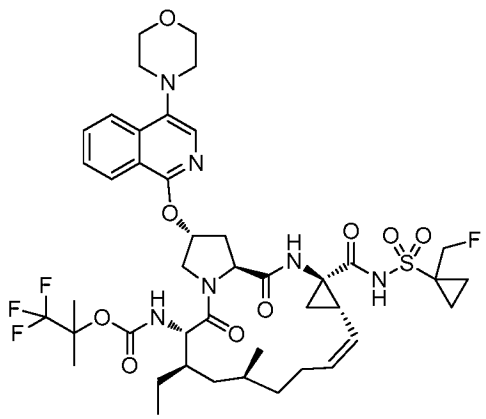
Compound 5443

Compounds 5442 and 5443 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

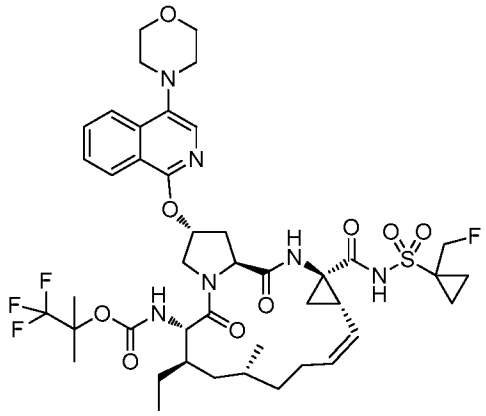
Compound 5442: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 841.6 (M^++1).

Compound 5443: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 841.6 (M^++1).

Preparation of Compound 5444 and Compound 5445



Compound 5444



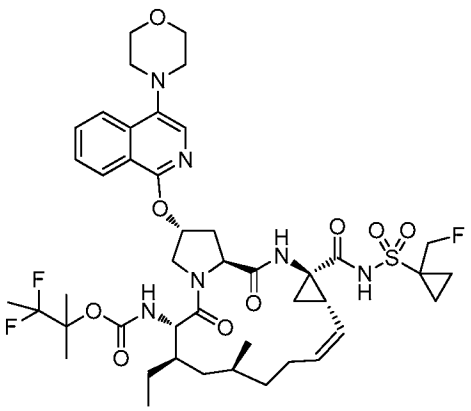
Compound 5445

Compounds 5444 and 5445 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

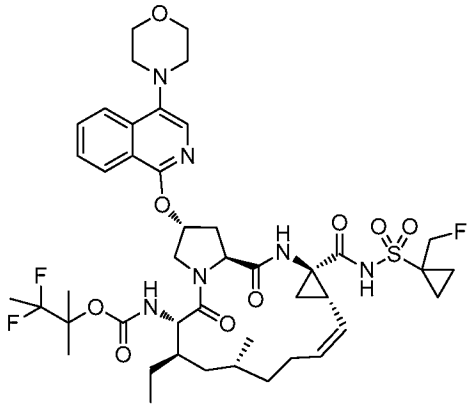
Compound 5444: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 909.8 (M^++1).

Compound 5445: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 909.9 (M^++1).

Preparation of Compound 5446 and Compound 5447



Compound 5446



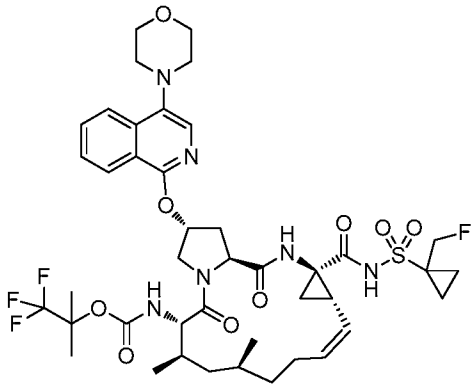
Compound 5447

Compounds 5446 and 5447 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

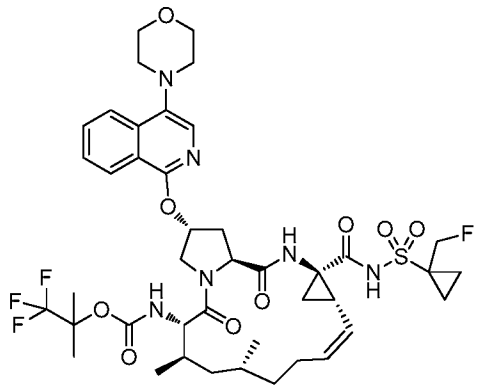
Compound 5446: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 905.6 (M^++1).

Compound 5447: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 905.7 (M^++1).

Preparation of Compound 5448 and Compound 5449



Compound 5448



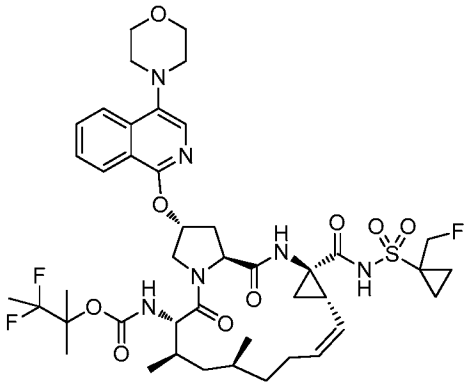
Compound 5449

Compounds 5448 and 5449 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

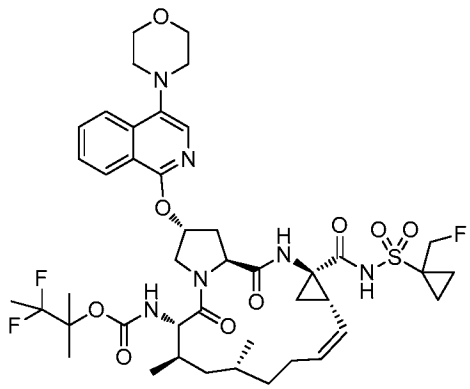
Compound 5448: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 895.8 (M^++1).

Compound 5449: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 895.9 (M^++1).

Preparation of Compound 5450 and Compound 5451



Compound 5450



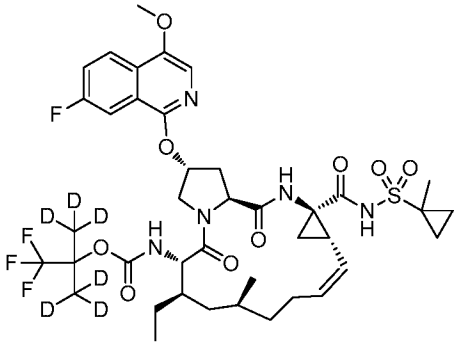
Compound 5451

Compounds 5450 and 5451 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

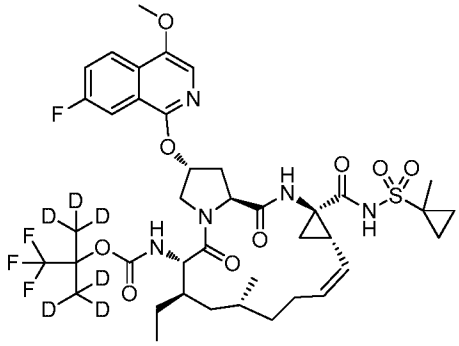
Compound 5450: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 891.9 (M^++1).

Compound 5451: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 891.9 (M^++1).

Preparation of Compound 5452 and Compound 5453



Compound 5452



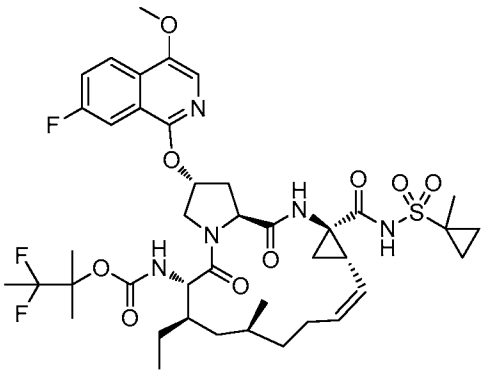
Compound 5453

Compounds 5452 and 5453 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

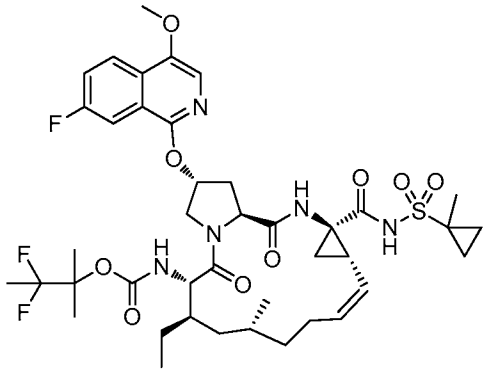
Compound 5452: MS: MS m/z 860.6 (M^++1).

Compound 5453: MS: MS m/z 860.6 (M^++1).

Preparation of Compound 5454 and Compound 5455



Compound 5454



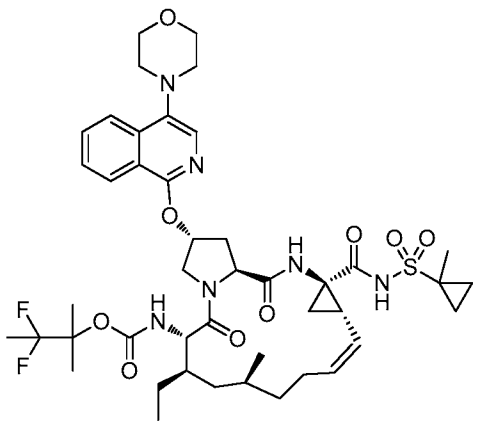
Compound 5455

Compounds 5454 and 5455 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

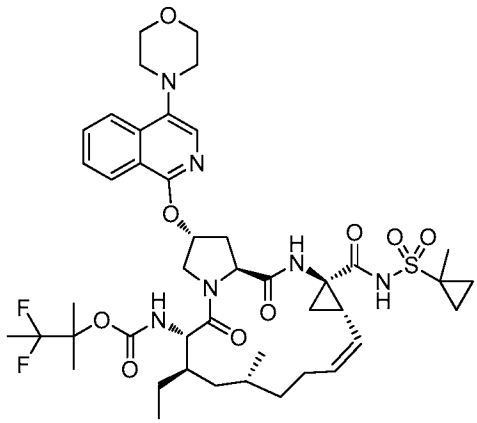
Compound 5454: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 850.9 (M^++1).

Compound 5455: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 850.9 (M^++1).

Preparation of Compound 5456 and Compound 5457



Compound 5456



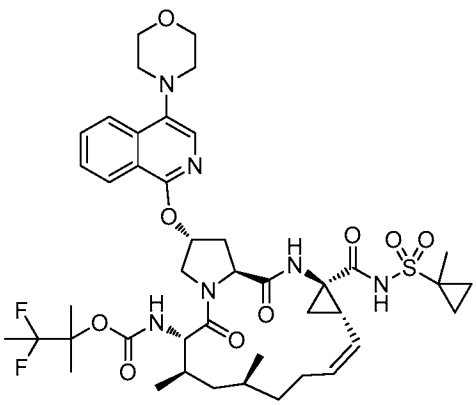
Compound 5457

Compounds 5456 and 5457 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

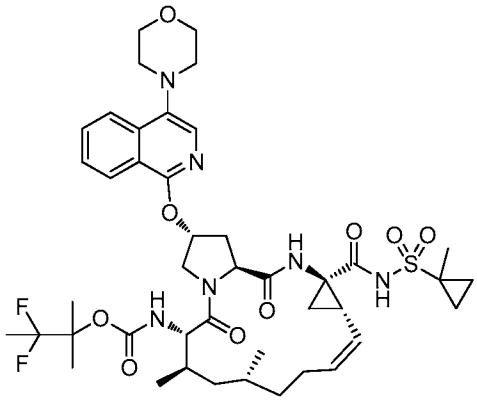
Compound 5456: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 888.1 (M^++1).

Compound 5457: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 888.0 (M^++1).

Preparation of Compound 5458 and Compound 5459



Compound 5458



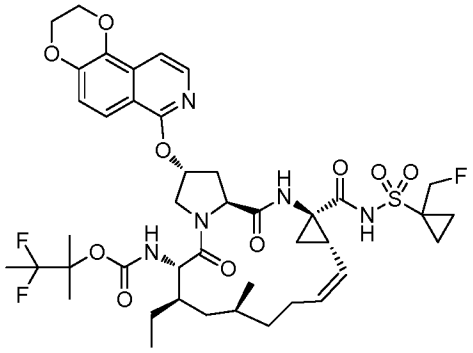
Compound 5459

Compounds 5458 and 5459 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

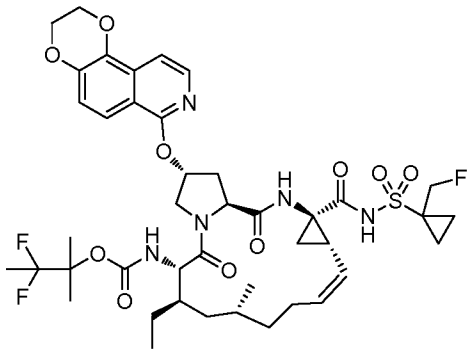
Compound 5458: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 874.1 (M^++1).

Compound 5459: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.11 (br. s., 1H), 8.11 (dd, *J*=15.1, 8.4 Hz, 2H), 7.83 - 7.74 (m, 2H), 7.64 - 7.55 (m, 2H), 5.80 (br. s., 1H), 5.53 (br. s., 1H), 4.98 (t, *J*=9.5 Hz, 1H), 4.62 - 4.49 (m, 2H), 3.95 - 3.90 (m, 1H), 3.86 (t, *J*=4.7 Hz, 3H), 3.71 (dd, *J*=10.7, 8.5 Hz, 1H), 3.08 - 2.95 (m, 4H), 2.76 - 2.59 (m, 2H), 2.40 - 2.27 (m, 2H), 1.96 - 1.78 (m, 2H), 1.74 - 1.66 (m, 1H), 1.64 - 1.09 (m, 16H), 0.97 - 0.88 (m, 10H), 0.76 (t, *J*=12.5 Hz, 1H). MS: MS m/z 874.0 (M^++1).

Preparation of Compound 5460 and Compound 5461



Compound 5460



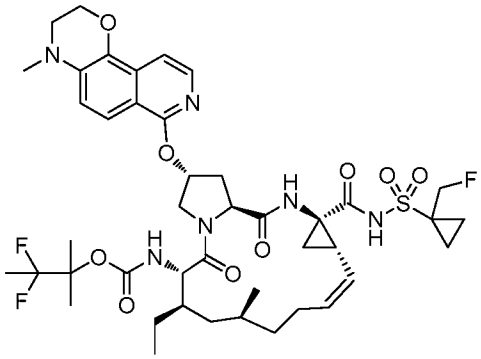
Compound 5461

Compounds 5460 and 5461 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

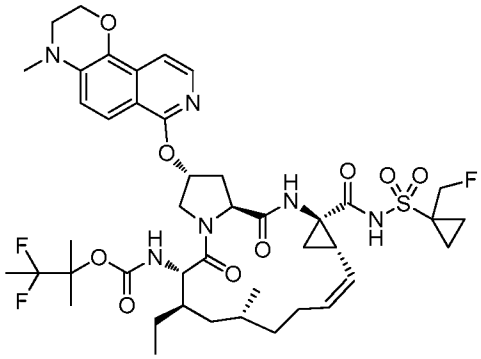
Compound 5460: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 878.6 (M^++1).

Compound 5461: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 878.7 (M^++1).

Preparation of Compound 5462 and Compound 5463



Compound 5462



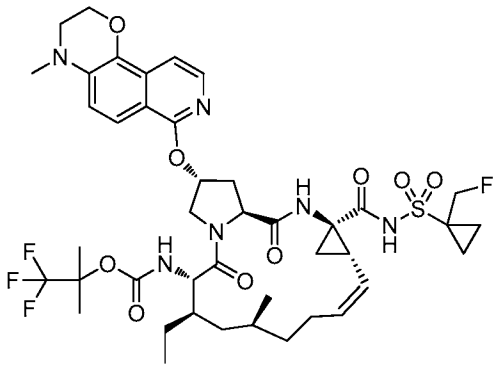
Compound 5463

Compounds 5462 and 5463 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

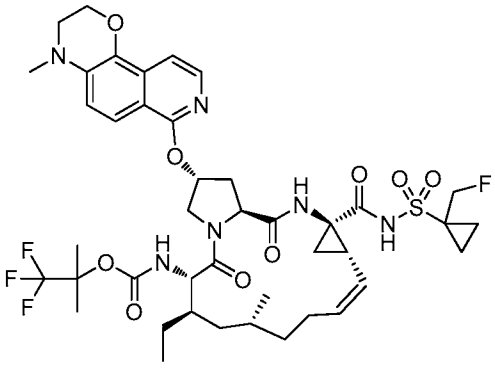
Compound 5462: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 891.6 (M^++1).

Compound 5463: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 891.7 (M^++1).

Preparation of Compound 5464 and Compound 5465



Compound 5464



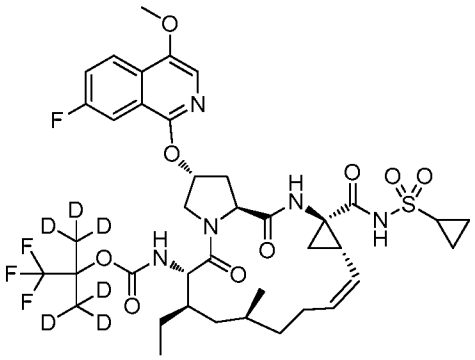
Compound 5465

Compounds 5464 and 5465 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

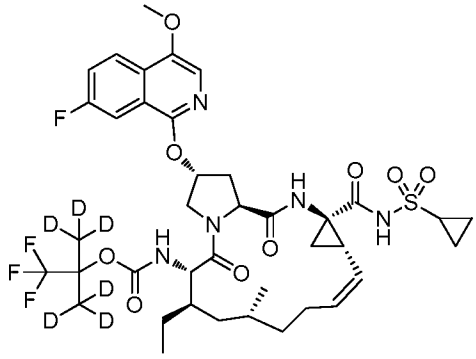
Compound 5464: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 895.7 (M^++1).

Compound 5465: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 895.7 (M^++1).

Preparation of Compound 5466 and Compound 5467



Compound 5466



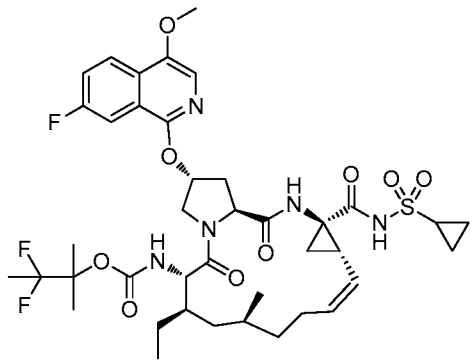
Compound 5467

Compounds 5466 and 5467 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

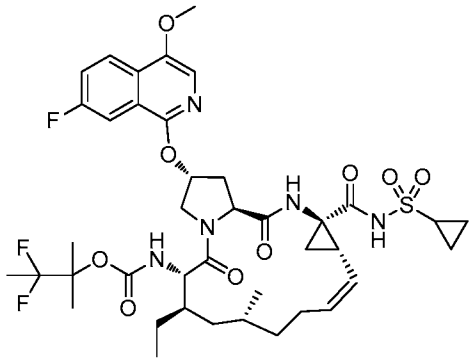
Compound 5466: MS: MS m/z 846.7 (M^++1).

Compound 5467: ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.98 (s, 1H), 8.15 (dd, *J*=9.0, 5.3 Hz, 1H), 7.87 (d, *J*=8.2 Hz, 1H), 7.74 - 7.64 (m, 3H), 5.77 (br. s., 1H), 5.58 - 5.49 (m, 1H), 5.06 (t, *J*=9.8 Hz, 1H), 4.57 - 4.46 (m, 2H), 3.99 (s, 3H), 3.93 - 3.84 (m, 2H), 2.96 - 2.88 (m, 1H), 2.73 - 2.60 (m, 2H), 2.36 - 2.25 (m, 2H), 2.01 - 1.84 (m, 2H), 1.65 - 1.32 (m, 7H), 1.21 - 0.91 (m, 10H), 0.74 (t, *J*=7.5 Hz, 3H). MS: MS m/z 846.7 (M^++1).

Preparation of Compound 5468 and Compound 5469



Compound 5468



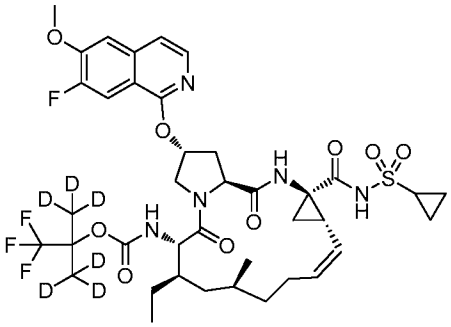
Compound 5469

Compounds 5468 and 5469 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

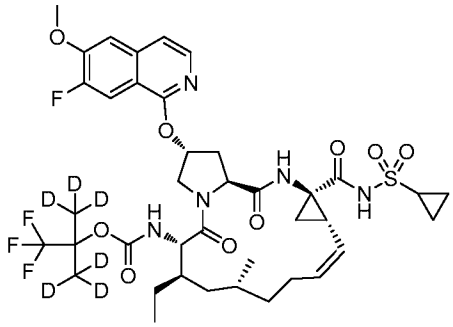
Compound 5468: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 836.7 (M^++1).

Compound 5469: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.19 (s, 1H), 8.97 (br. s., 1H), 8.15 (dd, *J*=9.2, 5.2 Hz, 1H), 7.76 - 7.57 (m, 4H), 5.77 (br. s., 1H), 5.53 (d, *J*=7.0 Hz, 1H), 5.06 (t, *J*=9.6 Hz, 1H), 4.60 - 4.45 (m, 2H), 3.99 (s, 3H), 3.94 - 3.80 (m, 2H), 2.91 (d, *J*=7.3 Hz, 1H), 2.75 - 2.60 (m, 2H), 2.35 - 2.25 (m, 2H), 1.93 (d, *J*=4.9 Hz, 2H), 1.65 - 1.31 (m, 10H), 1.27 - 0.90 (m, 15H), 0.74 (t, *J*=7.5 Hz, 3H). MS: MS m/z 836.7 (M^++1).

Preparation of Compound 5470 and Compound 5471



Compound 5470



Compound 5471

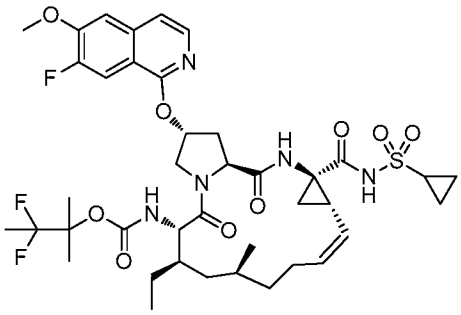
Compounds 5470 and 5471 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5470: MS: MS m/z 846.7 (M^++1).

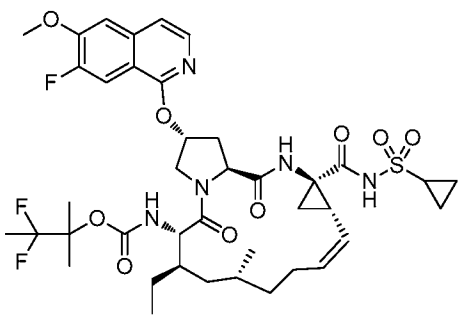
Compound 5471: ^{1}H NMR (500MHz, DMSO-d_6) δ 11.17 (s, 1H), 8.97 (br. s., 1H), 8.01 (d, *J*=5.8 Hz, 1H), 7.89 (d, *J*=7.9 Hz, 1H), 7.70 (d, *J*=11.6 Hz, 1H), 7.58 (d, *J*=8.5 Hz, 1H), 7.37 (d, *J*=5.8 Hz, 1H), 5.82 (br. s., 1H), 5.53 (d, *J*=6.1 Hz, 1H), 5.07 (t, *J*=10.1 Hz, 1H), 4.55 - 4.46 (m, 2H), 4.00 (s, 3H), 3.93 - 3.87 (m, 2H), 2.91 (d,

J=6.4 Hz, 1H), 2.72 - 2.60 (m, 2H), 2.36 - 2.26 (m, 2H), 2.01 - 1.86 (m, 2H), 1.64 - 1.32 (m, 7H), 1.23 - 0.90 (m, 9H), 0.74 (t, *J*=7.5 Hz, 3H). MS: MS m/z 846.7 (M^++1).

Preparation of Compound 5472 and Compound 5473



Compound 5472



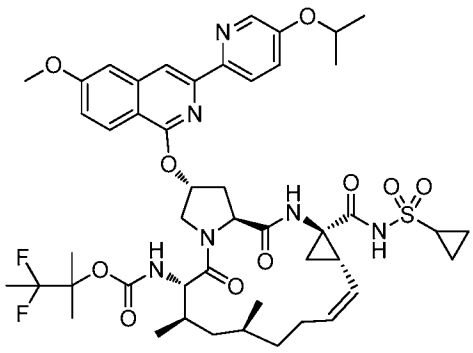
Compound 5473

Compounds 5472 and 5473 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

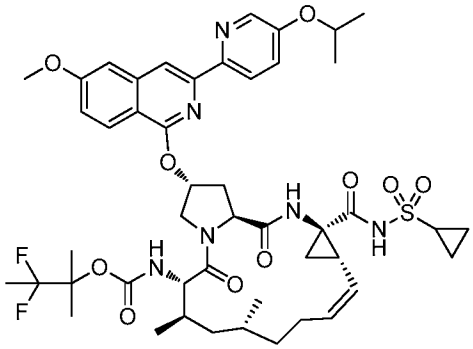
Compound 5472: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 836.7 (M^++1).

Compound 5473: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.95 (s, 1H), 8.00 (d, *J*=6.1 Hz, 1H), 7.74 - 7.64 (m, 2H), 7.58 (d, *J*=8.2 Hz, 1H), 7.37 (d, *J*=5.8 Hz, 1H), 5.82 (br. s., 1H), 5.58 - 5.47 (m, 1H), 5.07 (t, *J*=9.8 Hz, 1H), 4.57 - 4.44 (m, 2H), 3.99 (s, 3H), 3.94 - 3.87 (m, 2H), 2.99 - 2.87 (m, 1H), 2.76 - 2.60 (m, 2H), 2.36 - 2.26 (m, 2H), 1.93 (d, *J*=7.3 Hz, 2H), 1.65 - 0.91 (m, 25H), 0.75 (t, *J*=7.5 Hz, 3H). MS: MS m/z 836.6 (M^++1).

Preparation of Compound 5474 and Compound 5475



Compound 5474



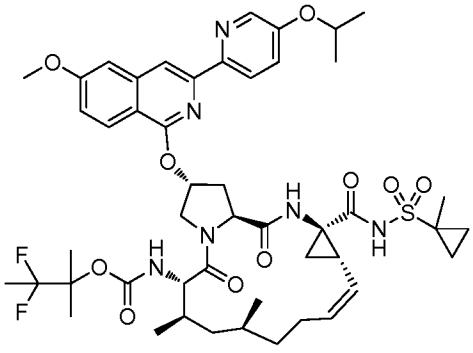
Compound 5475

Compounds 5474 and 5475 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

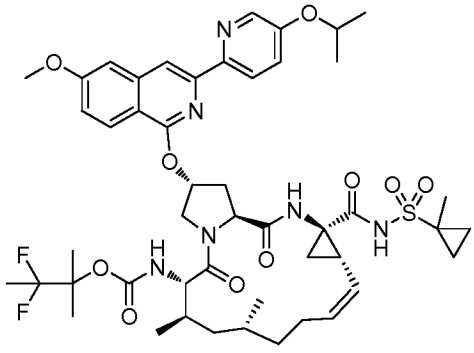
Compound 5474: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 939.7 (M^++1).

Compound 5475: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 939.7 (M^++1).

Preparation of Compound 5476 and Compound 5477



Compound 5476



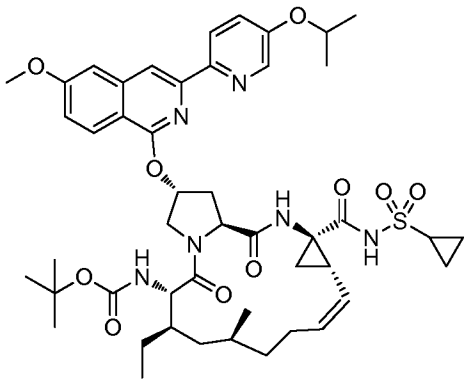
Compound 5477

Compounds 5476 and 5477 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

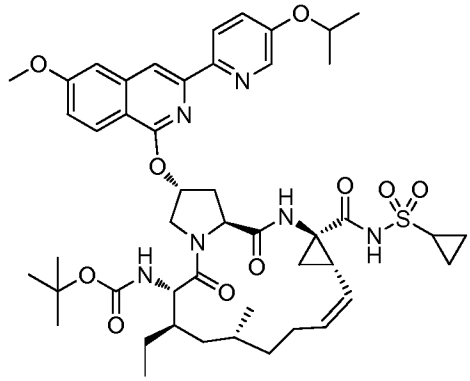
Compound 5476: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 953.8 (M^++1).

Compound 5477: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 953.7 (M^++1).

Preparation of Compound 5478 and Compound 5479



Compound 5478



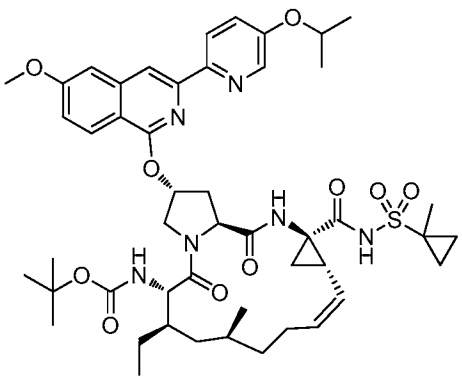
Compound 5479

Compounds 5478 and 5479 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

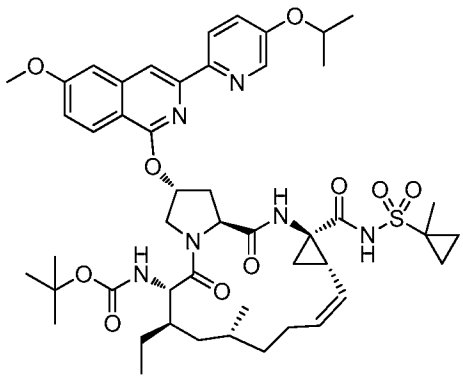
Compound 5478: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 903.7 (M^++1).

Compound 5479: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 903.7 (M^++1).

Preparation of Compound 5480 and Compound 5481



Compound 5480



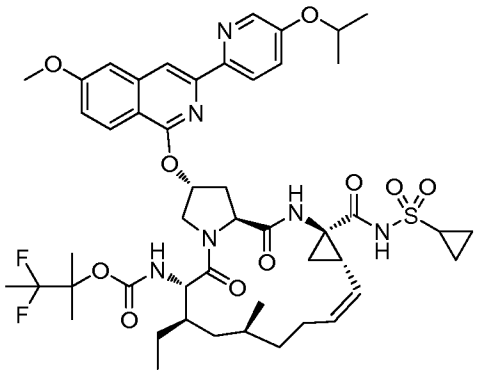
Compound 5481

Compounds 5480 and 5481 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

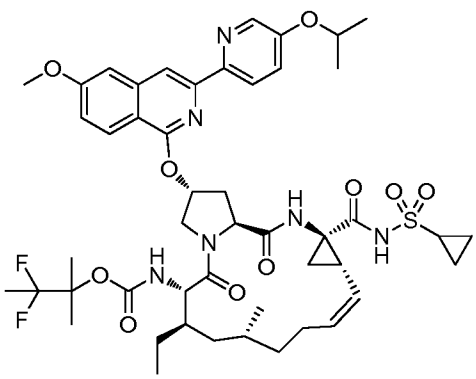
Compound 5480: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 917.7 (M^++1).

Compound 5481: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 917.7 (M^++1).

Preparation of Compound 5482 and Compound 5483



Compound 5482



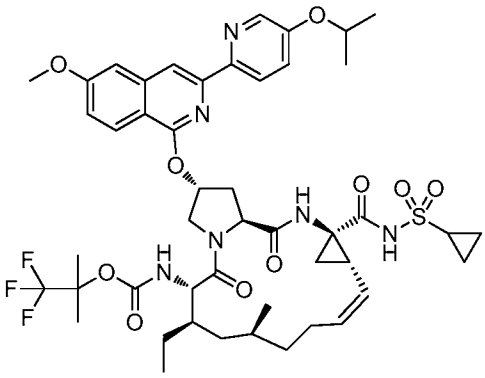
Compound 5483

Compounds 5482 and 5483 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

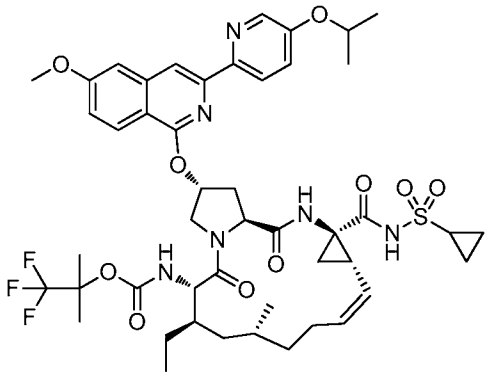
Compound 5482: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 953.7 (M^++1).

Compound 5483: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 953.7 (M^++1).

Preparation of Compound 5484 and Compound 5485



Compound 5484



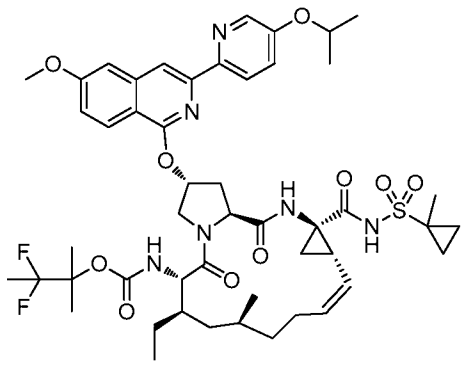
Compound 5485

Compounds 5484 and 5485 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

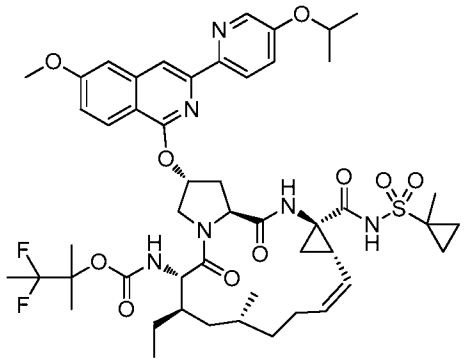
Compound 5484: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 957.7 (M^++1).

Compound 5485: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 957.7 (M^++1).

Preparation of Compound 5486 and Compound 5487



Compound 5486



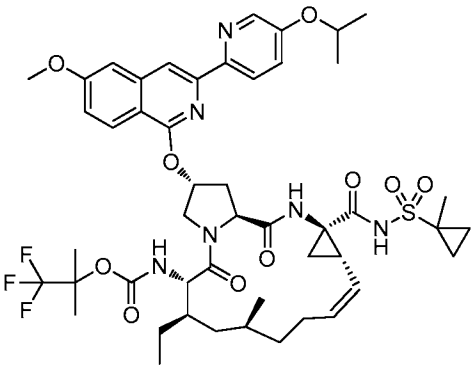
Compound 5487

Compounds 5486 and 5487 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

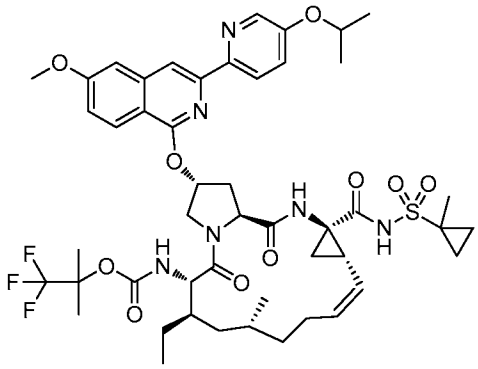
Compound 5486: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 967.8 (M^++1).

Compound 5487: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.40 - 8.32 (m, 2H), 8.24 (s, 1H), 8.00 (d, *J*=8.9 Hz, 1H), 7.64 (d, *J*=8.2 Hz, 1H), 7.56 (dd, *J*=8.7, 2.9 Hz, 1H), 7.44 (d, *J*=2.1 Hz, 1H), 7.10 (dd, *J*=9.0, 2.3 Hz, 1H), 6.02 (br. s., 1H), 5.52 (d, *J*=6.4 Hz, 1H), 5.02 (br. s., 1H), 4.78 (dt, *J*=11.7, 6.0 Hz, 1H), 4.57 - 4.47 (m, 2H), 4.02 (d, *J*=7.9 Hz, 1H), 3.98 - 3.89 (m, 4H), 2.75 - 2.62 (m, 2H), 2.42 - 2.26 (m, 2H), 1.98 - 1.87 (m, 2H), 1.64 - 1.15 (m, 16H), 1.09 (s, 2H), 1.01 (t, *J*=12.4 Hz, 1H), 0.95 - 0.83 (m, 5H), 0.73 (t, *J*=7.3 Hz, 3H). MS: MS m/z 967.7 (M^++1).

Preparation of Compound 5488 and Compound 5489



Compound 5488



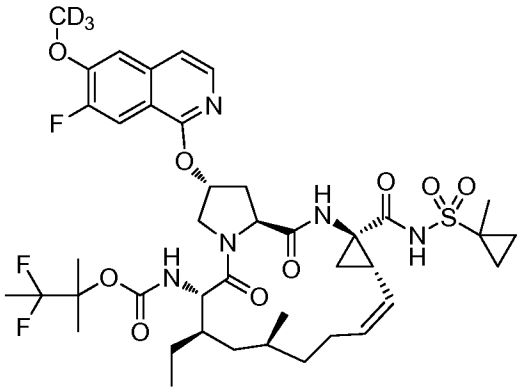
Compound 5489

Compounds 5488 and 5489 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5488: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 971.7 (M^++1).

Compound 5489: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.39 - 8.33 (m, 2H), 8.24 (s, 1H), 8.00 (d, *J*=9.2 Hz, 1H), 7.85 (d, *J*=8.9 Hz, 1H), 7.56 (dd, *J*=8.5, 2.7 Hz, 1H), 7.44 (d, *J*=2.1 Hz, 1H), 7.11 (dd, *J*=9.0, 2.3 Hz, 1H), 6.03 (br. s., 1H), 5.51 (d, *J*=6.7 Hz, 1H), 5.03 (br. s., 1H), 4.79 (dt, *J*=12.0, 6.1 Hz, 1H), 4.57 - 4.49 (m, 2H), 4.01 (d, *J*=7.9 Hz, 1H), 3.96 - 3.88 (m, 4H), 2.75 - 2.59 (m, 2H), 2.41 - 2.25 (m, 2H), 2.00 - 1.85 (m, 2H), 1.63 - 1.14 (m, 25H), 1.05 - 0.81 (m, 6H), 0.72 (t, *J*=7.3 Hz, 3H). MS: MS m/z 971.7 (M^++1).

Preparation of Compound 5501

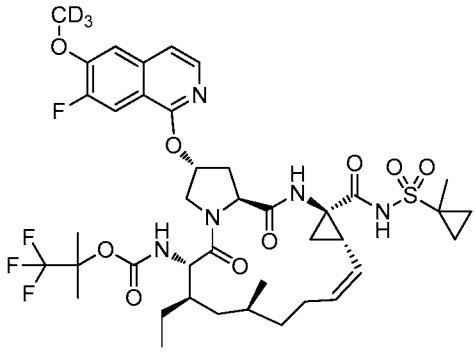


Compound 5501

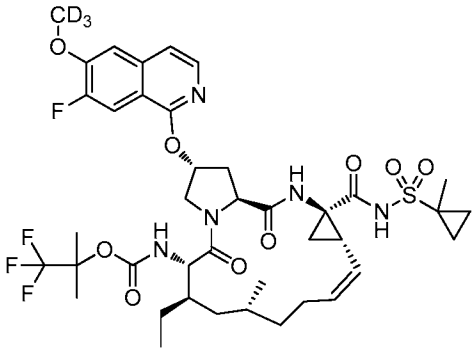
Compound 5501 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5501: MS: MS m/z 853.7 (M^++1).

Preparation of Compound 5502 and Compound 5503



Compound 5502



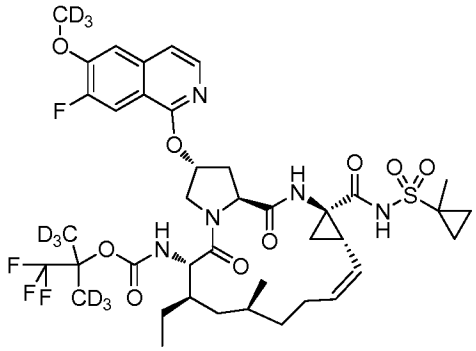
Compound 5503

Compounds 5502 and 5503 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

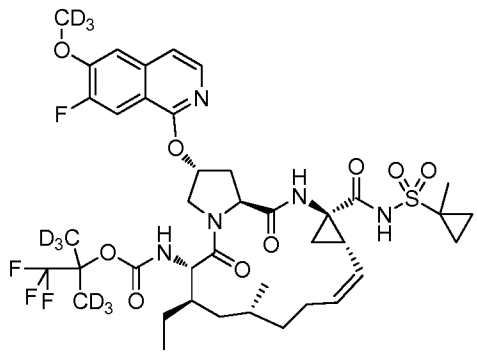
Compound 5502: MS: MS m/z 857.7 (M^++1).

Compound 5503: ^{1}H NMR (500MHz, DMSO-d_6) δ 7.98 (d, *J*=5.8 Hz, 1H), 7.83 (d, *J*=8.2 Hz, 1H), 7.69 (d, *J*=11.6 Hz, 1H), 7.54 (d, *J*=8.5 Hz, 1H), 7.35 (d, *J*=5.8 Hz, 1H), 5.81 (br. s., 1H), 5.50 (d, *J*=6.1 Hz, 1H), 5.04 (br. s., 1H), 4.50 (d, *J*=10.1 Hz, 2H), 3.94 - 3.85 (m, 2H), 2.60 (d, *J*=6.1 Hz, 2H), 2.34 - 2.24 (m, 2H), 1.91 (t, *J*=14.5 Hz, 2H), 1.61 - 0.80 (m, 25H), 0.72 (t, *J*=7.5 Hz, 3H). MS: MS m/z 857.7 (M^++1).

Preparation of Compound 5504 and Compound 5505



Compound 5504



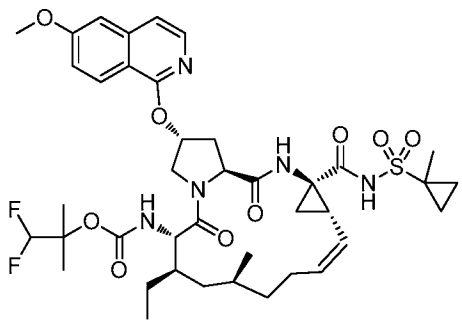
Compound 5505

Compounds 5504 and 5505 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

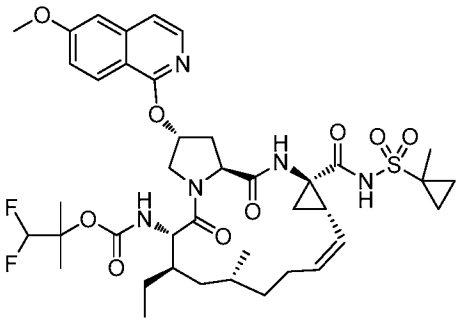
Compound 5504: MS: MS m/z 863.8 (M^++1).

Compound 5505: MS: MS m/z 863.7 (M^++1).

Preparation of Compound 5522 and Compound 5523



Compound 5522



Compound 5523

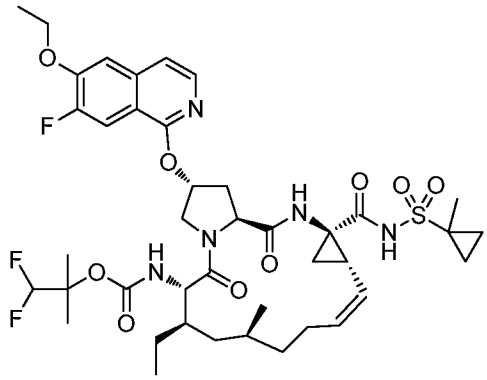
Compounds 5522 and 5523 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5522: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 818.8 (M^++1).

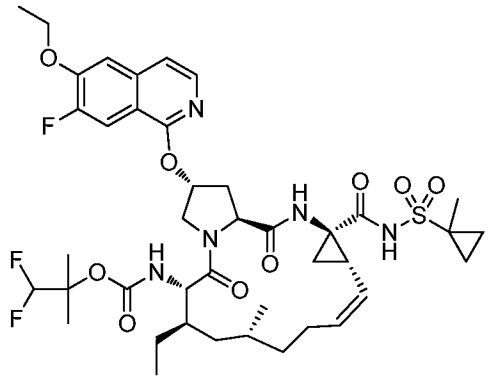
Compound 5523: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-methoxyisoquinolin-1-yl)oxy)-9-

methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.05 - 7.91 (m, 2H), 7.66 (d, *J*=8.5 Hz, 1H), 7.35 - 7.26 (m, 2H), 7.13 (dd, *J*=9.2, 2.4 Hz, 1H), 5.92 - 5.65 (m, 2H), 5.54 - 5.44 (m, 1H), 5.09 (br. s., 1H), 4.61 - 4.45 (m, 2H), 3.89 (s, 5H), 2.62 - 2.53 (m, 2H), 2.35 - 2.24 (m, 2H), 1.97 - 1.83 (m, 2H), 1.59 - 0.75 (m, 25H), 0.71 (t, *J*=7.5 Hz, 3H). MS: MS m/z 818.8 (M^++1).

Preparation of Compound 5524 and Compound 5525



Compound 5524



Compound 5525

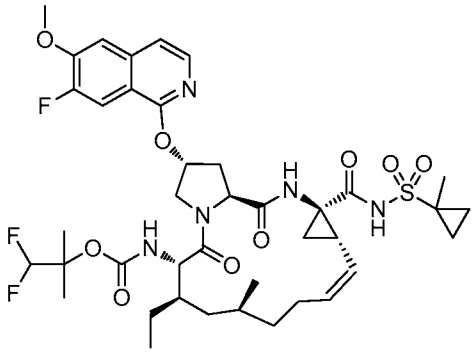
Compounds 5524 and 5525 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5524: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 850.8 (M^++1).

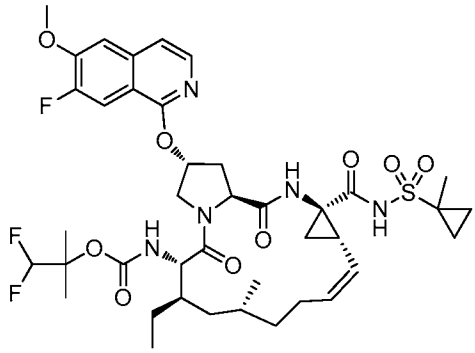
Compound 5525: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 7.95 (d, *J*=5.8 Hz, 1H), 7.74 - 7.61 (m, 2H), 7.51 (d, *J*=8.2 Hz, 1H), 7.33 (d, *J*=5.5 Hz, 1H), 5.86 - 5.60 (m, 2H), 5.50 (d, *J*=5.5 Hz, 1H), 4.99 (br. s., 1H), 4.59 - 4.46 (m, 2H), 4.28 - 4.18 (m, 2H), 3.93 - 3.80 (m, 2H), 2.62 (br. s., 2H), 2.29 (d, *J*=5.2 Hz,

2H), 1.89 (d, *J*=10.4 Hz, 2H), 1.59 (br. s., 1H), 1.52 - 0.94 (m, 22H), 0.93 - 0.82 (m, 5H), 0.69 (t, *J*=7.3 Hz, 3H). MS: MS m/z 850.8 (M^++1).

Preparation of Compound 5526 and Compound 5527



Compound 5526



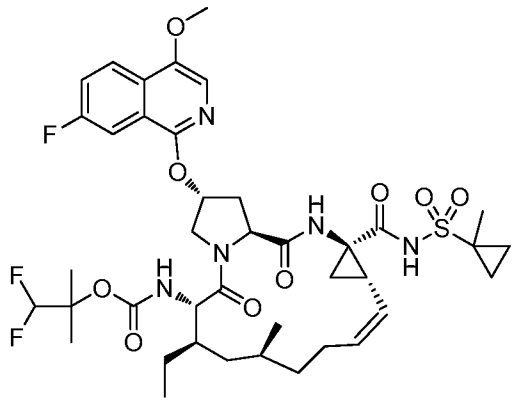
Compound 5527

Compounds 5526 and 5527 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

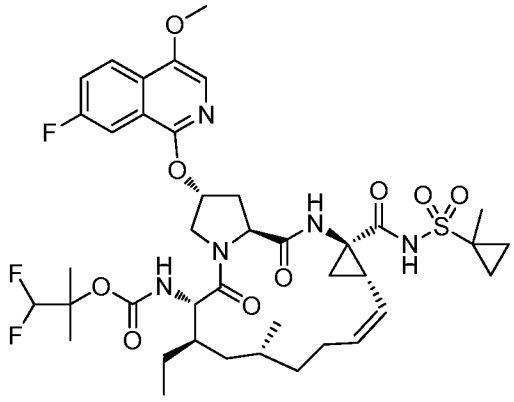
Compound 5526: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 836.8 (M^++1).

Compound 5527: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 7.99 (d, *J*=5.8 Hz, 1H), 7.77 - 7.65 (m, 2H), 7.56 (d, *J*=8.2 Hz, 1H), 7.36 (d, *J*=6.1 Hz, 1H), 5.90 - 5.60 (m, 2H), 5.52 (d, *J*=6.4 Hz, 1H), 4.98 (br. s., 1H), 4.59 - 4.49 (m, 2H), 3.98 (s, 3H), 3.93 - 3.81 (m, 2H), 2.72 - 2.59 (m, 2H), 2.39 - 2.25 (m, 2H), 1.92 (d, *J*=9.8 Hz, 2H), 1.61 (br. s., 1H), 1.56 - 0.96 (m, 19H), 0.95 - 0.84 (m, 5H), 0.71 (t, *J*=7.5 Hz, 3H). MS: MS m/z 836.8 (M^++1).

Preparation of Compound 5528 and Compound 5529



Compound 5528



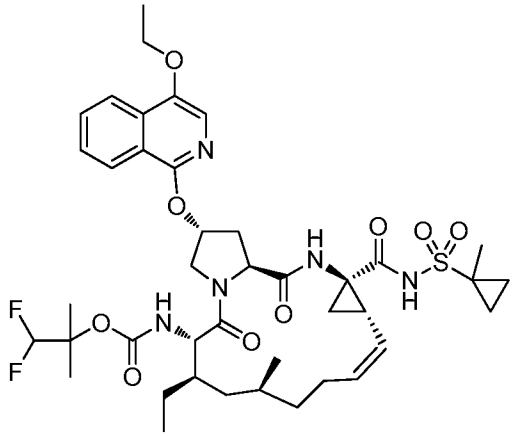
Compound 5529

Compounds 5528 and 5529 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

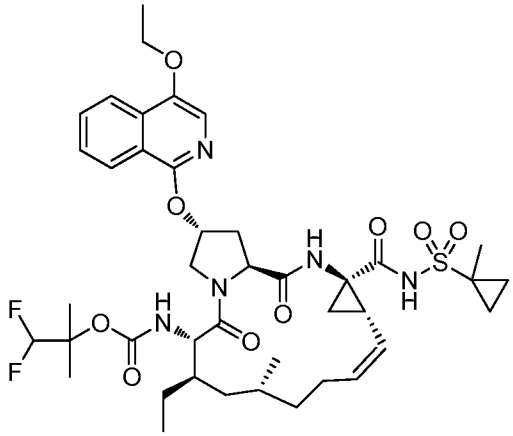
Compound 5528: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 836.8 (M^++1).

Compound 5529: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.16 - 8.10 (m, 1H), 7.75 - 7.61 (m, 4H), 5.90 - 5.62 (m, 2H), 5.52 (br. s., 1H), 4.97 (br. s., 1H), 4.61 - 4.50 (m, 2H), 3.98 (s, 3H), 3.93 - 3.81 (m, 2H), 2.72 - 2.58 (m, 2H), 2.31 (d, *J*=10.1 Hz, 2H), 1.92 (br. s., 2H), 1.61 (br. s., 1H), 1.56 - 0.98 (m, 19H), 0.94 - 0.87 (m, 5H), 0.71 (t, *J*=7.2 Hz, 3H). MS: MS m/z 836.8 (M^++1).

Preparation of Compound 5530 and Compound 5531



Compound 5530



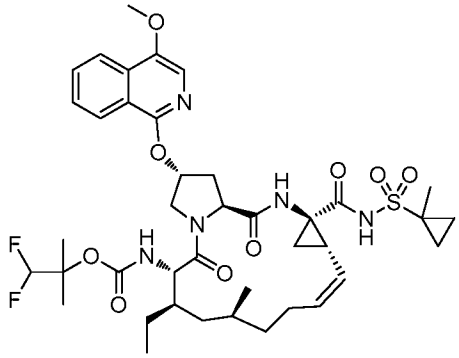
Compound 5531

Compounds 5530 and 5531 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

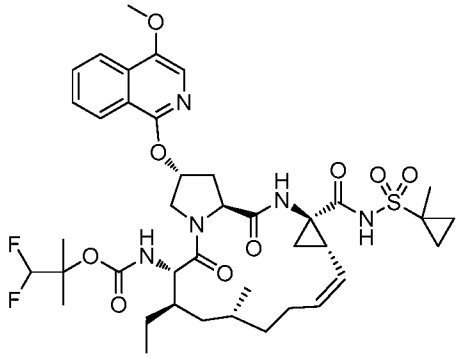
Compound 5530: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 832.8 (M^++1).

Compound 5531: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.09 - 8.02 (m, 2H), 7.79 (t, *J*=7.8 Hz, 1H), 7.70 - 7.57 (m, 3H), 5.93 - 5.64 (m, 2H), 5.56 - 5.47 (m, 1H), 4.98 (br. s., 1H), 4.63 - 4.49 (m, 2H), 4.20 (q, *J*=6.8 Hz, 2H), 3.96 - 3.83 (m, 2H), 2.72 - 2.58 (m, 2H), 2.37 - 2.24 (m, 2H), 1.98 - 1.85 (m, 2H), 1.60 (d, *J*=7.3 Hz, 1H), 1.54 - 0.84 (m, 27H), 0.71 (t, *J*=7.5 Hz, 3H). MS: MS m/z 832.9 (M^++1).

Preparation of Compound 5532 and Compound 5533



Compound 5532



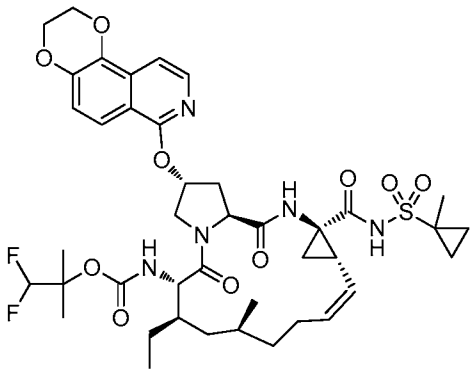
Compound 5533

Compounds 5532 and 5533 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

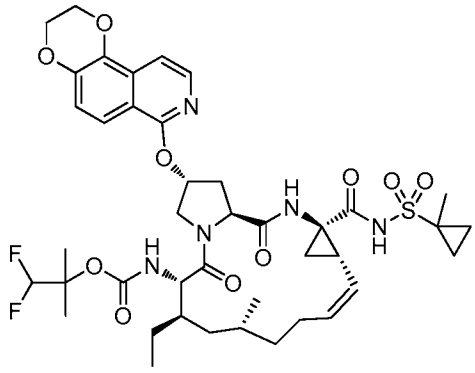
Compound 5532: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 818.8 (M^++1).

Compound 5533: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.06 (d, *J*=9.2 Hz, 2H), 7.79 (t, *J*=7.8 Hz, 1H), 7.71 - 7.57 (m, 3H), 5.92 - 5.65 (m, 2H), 5.52 (d, *J*=5.5 Hz, 1H), 4.97 (br. s., 1H), 4.63 - 4.47 (m, 2H), 3.97 (s, 3H), 3.94 - 3.84 (m, 2H), 2.72 - 2.57 (m, 2H), 2.37 - 2.24 (m, 2H), 2.00 - 1.84 (m, 2H), 1.61 (br. s., 1H), 1.53 - 0.85 (m, 24H), 0.71 (t, *J*=7.3 Hz, 3H). MS: MS m/z 818.7 (M^++1).

Preparation of Compound 5534 and Compound 5535



Compound 5534



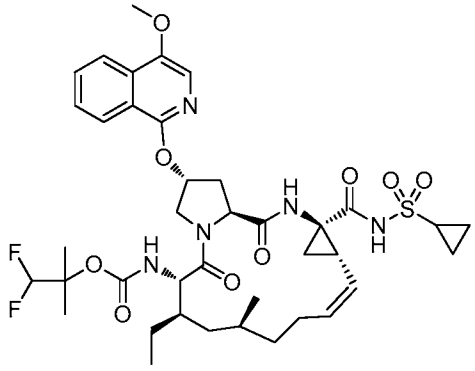
Compound 5535

Compounds 5534 and 5535 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

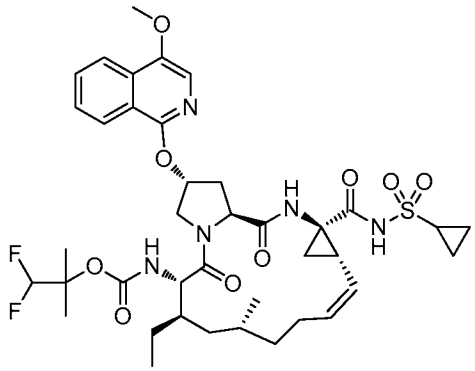
Compound 5534: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 846.7 (M^++1).

Compound 5535: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 7.96 (d, *J*=5.8 Hz, 1H), 7.66 (d, *J*=7.9 Hz, 1H), 7.59 (d, *J*=9.2 Hz, 1H), 7.37 (d, *J*=6.1 Hz, 1H), 7.10 (d, *J*=8.9 Hz, 1H), 5.85 - 5.57 (m, 2H), 5.55 - 5.49 (m, 1H), 4.96 (br. s., 1H), 4.62 - 4.31 (m, 6H), 3.94 - 3.80 (m, 2H), 2.71 - 2.57 (m, 2H), 2.29 (br. s., 2H), 1.91 (br. s., 2H), 1.61 (br. s., 1H), 1.55 - 0.85 (m, 22H), 0.70 (t, *J*=7.2 Hz, 3H). MS: MS m/z 846.7 (M^++1).

Preparation of Compound 5536 and Compound 5537



Compound 5536



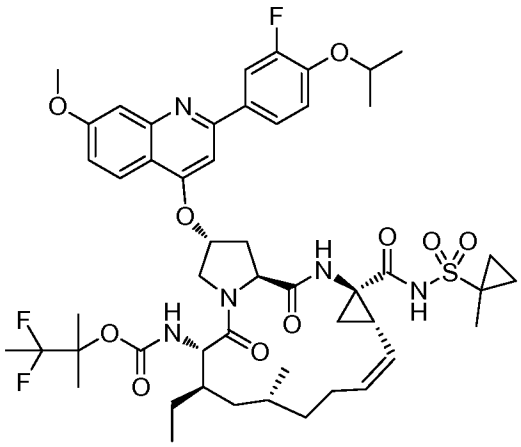
Compound 5537

Compounds 5536 and 5537 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5536: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 804.7 (M^++1).

Compound 5537: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.05 (d, *J*=8.2 Hz, 2H), 7.79 (t, *J*=7.9 Hz, 1H), 7.68 - 7.58 (m, 3H), 5.93 - 5.66 (m, 2H), 5.56 - 5.47 (m, 1H), 5.04 (br. s., 1H), 4.58 (d, *J*=11.6 Hz, 1H), 4.52 - 4.45 (m, 1H), 3.96 (s, 3H), 3.91 - 3.84 (m, 2H), 2.89 (br. s., 1H), 2.69 - 2.58 (m, 2H), 2.29 (br. s., 2H), 1.92 (d, *J*=7.3 Hz, 2H), 1.63 - 1.30 (m, 7H), 1.19 - 0.89 (m, 17H), 0.71 (t, *J*=7.3 Hz, 3H). MS: MS m/z 804.7 (M^++1).

Preparation of Compound 5550

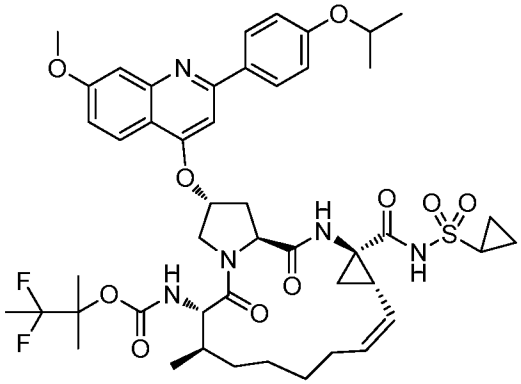


Compound 5550

Compound 5550 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5550: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((2-(3-fluoro-4-isopropoxyphenyl)-7-methoxyquinolin-4-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 985.0 (M^++1).

Preparation of Compound 5551



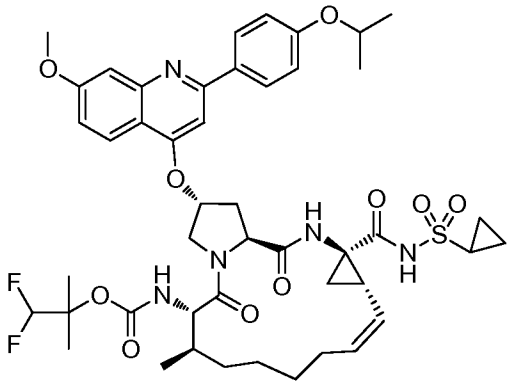
Compound 5551

Compounds 5551 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5551: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2-(4-isopropoxyphenyl)-7-

methoxyquinolin-4-yl)oxy)-7-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 924.9 (M^++1).

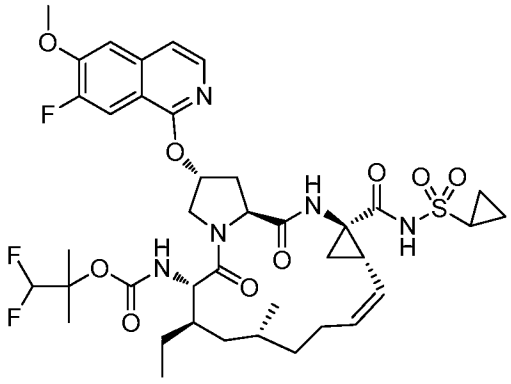
Preparation of Compound 5552



Compound 5552

Compound 5552 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117: Compound 5552: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2-(4-isopropoxyphenyl)-7-methoxyquinolin-4-yl)oxy)-7-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS m/z 910.9 (M^++1).

Preparation of Compound 5553

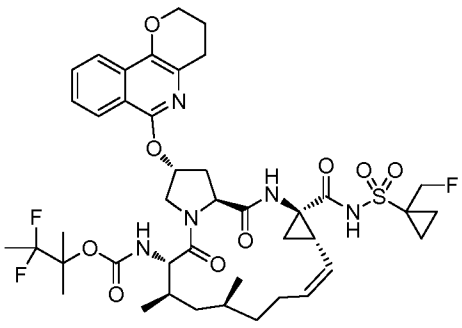


Compound 5553

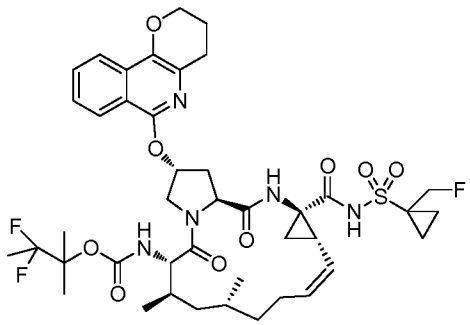
Compound 5553 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 5553: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.98 - 8.82 (m, 1H), 7.98 (d, *J*=5.8 Hz, 1H), 7.73 - 7.63 (m, 2H), 7.55 (d, *J*=8.5 Hz, 1H), 7.36 (d, *J*=5.8 Hz, 1H), 5.89 - 5.62 (m, 2H), 5.56 - 5.43 (m, 1H), 5.11 (br. s., 1H), 4.60 - 4.44 (m, 2H), 3.97 (s, 3H), 3.91 - 3.80 (m, 2H), 2.88 (br. s., 1H), 2.61 (d, *J*=7.3 Hz, 2H), 2.37 - 2.22 (m, 2H), 1.90 (d, *J*=10.4 Hz, 2H), 1.62 - 0.88 (m, 22H), 0.71 (t, *J*=7.3 Hz, 3H). MS: MS m/z 822.8 (M^++1).

Preparation of Compound 6039 and Compound 6040



Compound 6039



Compound 6040

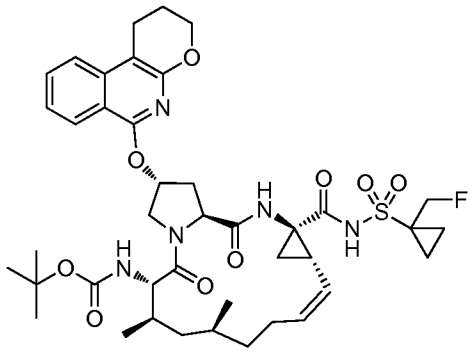
Compounds 6039 and 6040 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6039: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 862.58 (M^++1).

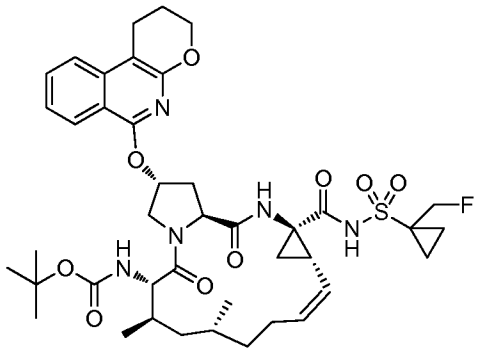
Compound 6040: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-

yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.26 (s, 1H), 8.99 (s, 1H), 8.06 (d, *J*=8.5 Hz, 1H), 7.95 (d, *J*=8.2 Hz, 1H), 7.74 (t, *J*=7.5 Hz, 1H), 7.64 (d, *J*=8.2 Hz, 1H), 7.51 (t, *J*=7.6 Hz, 1H), 5.74 (br. s., 1H), 5.52 (m, 1H), 5.01 (t, *J*=9.6 Hz, 1H), 4.87-4.76 (m, 1H), 4.60 - 4.39 (m, 3H), 4.33 - 4.19 (m, 2H), 4.01 - 3.87 (m, 1H), 3.81 - 3.68 (m, 1H), 2.97 - 2.81 (m, 2H), 2.77 - 2.59 (m, 2H), 2.34 - 2.23 (m, 2H), 2.17 - 2.04 (m, 2H), 1.99 - 1.78 (m, 2H), 1.69 - 1.38 (m, 10H), 1.34 (s, 3H), 1.30 - 1.21 (m, 3H), 1.12 (s, 3H), 0.93 (dd, *J*=18.2, 6.6 Hz, 6H), 0.76 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 862.58 (M^++1).

Preparation of Compound 6041 and Compound 6042



Compound 6041



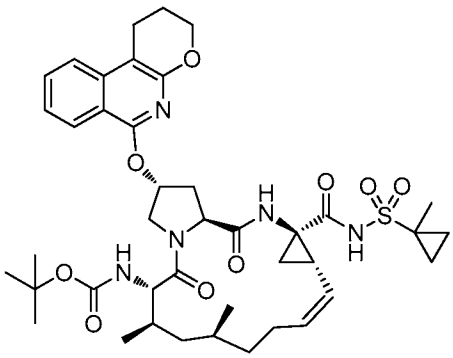
Compound 6042

Compounds 6041 and 6042 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

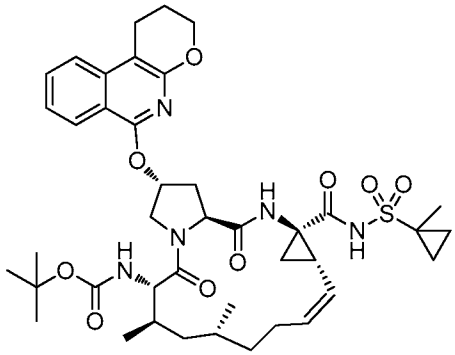
Compound 6041: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 812.8 (M^++1).

Compound 6042: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, METHANOL-d_4) δ 8.11 (d, *J*=8.2 Hz, 1H), 7.72 (d, *J*=8.2 Hz, 1H), 7.64 (t, *J*=7.5 Hz, 1H), 7.29 (t, *J*=7.5 Hz, 1H), 6.65 (d, *J*=8.5 Hz, 1H), 5.79 (br. s., 1H), 5.53 (td, *J*=10.1, 6.0 Hz, 1H), 5.07 (m, 1H), 4.76 (t, *J*=11.6 Hz, 1H), 4.67 - 4.47 (m, 2H), 4.41 - 4.23 (m, 2H), 4.01 (dd, *J*=11.7, 3.2 Hz, 1H), 3.87 (dd, *J*=10.5, 8.7 Hz, 1H), 2.97 - 2.85 (m, 2H), 2.77 - 2.58 (m, 2H), 2.50 - 2.32 (m, 2H), 2.21 - 2.10 (m, 2H), 2.04 - 1.86 (m, 1H), 1.86 - 1.73 (m, 2H), 1.71 - 1.59 (m, 3H), 1.53 (m, 1H), 1.48 - 1.34 (m, 2H), 1.29 - 1.11 (m, 11H), 1.09 (m, 1H), 0.99 (dd, *J*=9.8, 6.7 Hz, 6H), 0.81 (t, *J*=11.4 Hz, 1H); MS: MS *m/z* 812.8 (M^++1).

Preparation of Compound 6043 and Compound 6044



Compound 6043



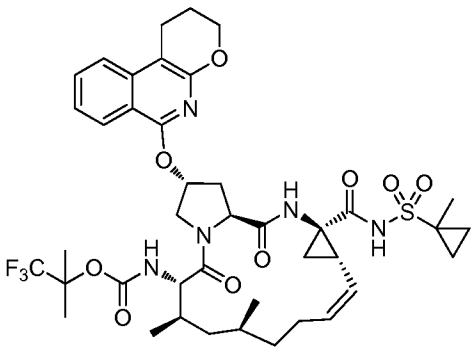
Compound 6044

Compounds 6043 and 6044 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

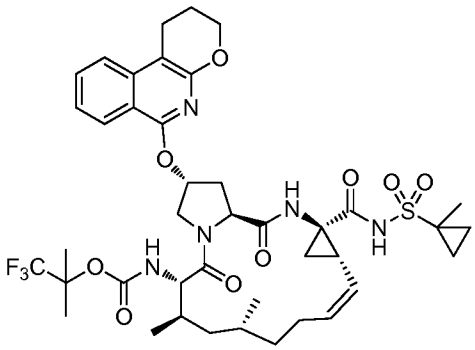
Compound 6043: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 794.8 (M^++1).

Compound 6044: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.08 (br. s., 1H), 8.07 (d, *J*=7.9 Hz, 1H), 7.83 - 7.63 (m, 2H), 7.31 (t, *J*=7.5 Hz, 1H), 7.20 (d, *J*=8.2 Hz, 1H), 5.70 (br. s., 1H), 5.52 (m, 1H), 5.05 - 4.94 (m, 1H), 4.63 (d, *J*=11.0 Hz, 1H), 4.48 - 4.39 (m, 1H), 4.28 (t, *J*=5.2 Hz, 2H), 3.93 - 3.85 (m, 1H), 3.72 (dd, *J*=10.5, 8.4 Hz, 1H), 2.87 (q, *J*=6.1 Hz, 2H), 2.70 (m, 1H), 2.67 - 2.57 (m, 1H), 2.40 - 2.21 (m, 2H), 2.05 (m, 2H), 1.95 - 1.86 (m, 1H), 1.82 (m, 1H), 1.69 (m, 1H), 1.60 (m, 1H), 1.51 (m, 1H), 1.41 (m, 6H), 1.36 (m, 1H), 1.32 - 1.24 (m, 1H), 1.14 (s, 9H), 1.03 (m, 1H), 0.96 - 0.86 (m, 8H), 0.74 (t, *J*=11.7 Hz, 1H); MS: MS *m/z* 794.8 (M^++1).

Preparation of Compound 6045 and Compound 6046



Compound 6045



Compound 6046

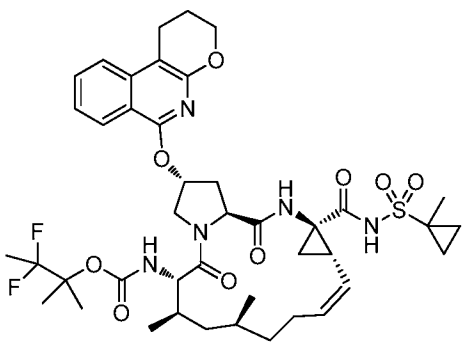
Compounds 6045 and 6046 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6045: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

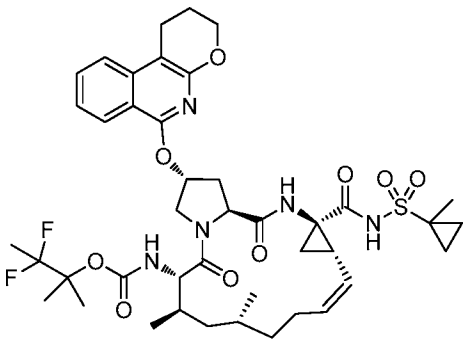
1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 848.8 (M^++1).

Compound 6046: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.12 (s, 1H), 8.04 (d, *J*=8.2 Hz, 1H), 7.84 (d, *J*=7.9 Hz, 1H), 7.78 - 7.74 (m, 1H), 7.73 - 7.67 (m, 1H), 7.34 (t, *J*=7.6 Hz, 1H), 5.71 (br. s., 1H), 5.57 - 5.48 (m, 1H), 4.98 (t, *J*=9.9 Hz, 1H), 4.60 (d, *J*=11.6 Hz, 1H), 4.50 (dd, *J*=10.2, 6.9 Hz, 1H), 4.28 (t, *J*=5.2 Hz, 2H), 3.96 - 3.86 (m, 2H), 3.70 (dd, *J*=10.7, 7.9 Hz, 1H), 2.87 (m, 2H), 2.74 - 2.60 (m, 2H), 2.41 - 2.25 (m, 2H), 2.11 - 2.01 (m, 2H), 1.97 - 1.79 (m, 2H), 1.70 (m, 1H), 1.64 - 1.59 (m, 1H), 1.56 - 1.50 (m, 1H), 1.48 - 1.39 (m, 5H), 1.35 (s, 3H), 1.29 (m, 1H), 1.14 (m 1H), 1.04 (s, 3H), 0.91 (dd, *J*=19.1, 6.6 Hz, 8H), 0.76 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 848.8 (M^++1).

Preparation of Compound 6047 and Compound 6048



Compound 6047



Compound 6048

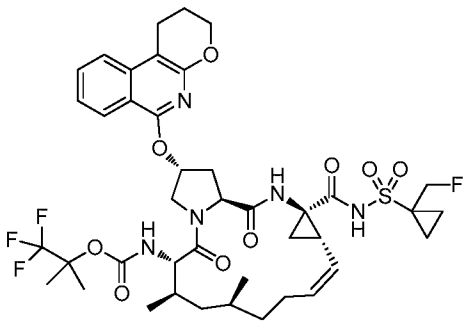
Compounds 6047 and 6048 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6047: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-

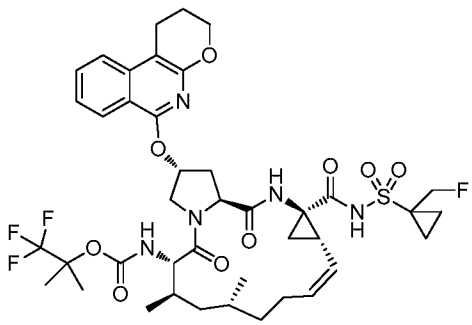
yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 844.8 (M^++1).

Compound 6048: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.04 (br. s., 1H), 9.09 (br. s., 1H), 8.04 (d, *J*=7.9 Hz, 1H), 7.76 (d, *J*=8.5 Hz, 1H), 7.72 - 7.67 (m, 1H), 7.62 (d, *J*=8.2 Hz, 1H), 7.33 (t, *J*=7.5 Hz, 1H), 5.71 (br. s., 1H), 5.53 (d, *J*=6.1 Hz, 1H), 4.99 (t, *J*=9.0 Hz, 1H), 4.59 (d, *J*=11.3 Hz, 1H), 4.48 (dd, *J*=10.1, 7.3 Hz, 1H), 4.28 (t, *J*=5.0 Hz, 2H), 3.95 - 3.87 (m, 2H), 3.71 (dd, *J*=10.7, 8.2 Hz, 1H), 2.87 (m, 2H), 2.71 (m, 1H), 2.68 - 2.58 (m, 1H), 2.39 - 2.26 (m, 2H), 2.10 - 1.99 (m, 2H), 1.95 - 1.78 (m, 2H), 1.70 (m, 1H), 1.56 (m, 5H), 1.41 (m, 5H), 1.37 (m, 1H), 1.28 (s, 3H), 1.16 (m, 1H), 0.98 (s, 3H), 0.92 (dd, *J*=16.5, 6.7 Hz, 8H), 0.76 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 844.8 (M^++1).

Preparation of Compound 6049 and Compound 6050



Compound 6049



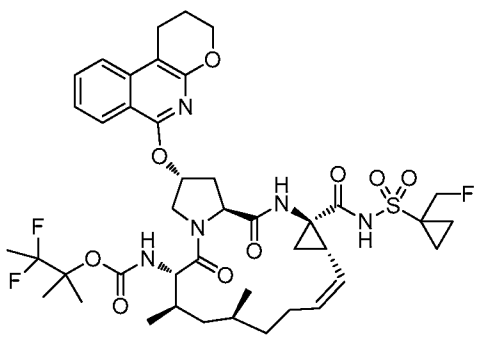
Compound 6050

Compounds 6049 and 6050 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

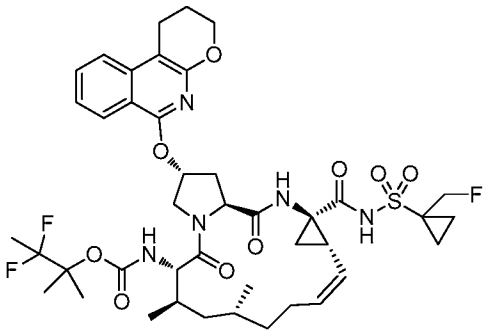
Compound 6049: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 866.8 (M^++1).

Compound 6050: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.22 (s, 1H), 9.09 (s, 1H), 8.08 (d, *J*=8.2 Hz, 1H), 7.82 - 7.69 (m, 3H), 7.34 (t, *J*=7.2 Hz, 1H), 5.70 (br. s., 1H), 5.62 (m, 1H), 5.05 (t, *J*=9.5 Hz, 1H), 4.74- (d, *J*=11.3 Hz, 1H), 4.59 (d, *J*=11.6 Hz, 1H), 4.54 - 4.47 (m, 1H), 4.39 (d, *J*=12.2 Hz, 1H), 4.29 (t, *J*=5.0 Hz, 2H), 4.01 (t, *J*=6.6 Hz, 1H), 3.93 (d, *J*=8.2 Hz, 1H), 2.92 - 2.86 (m, 2H), 2.69 - 2.58 (m, 1H), 2.41 - 2.21 (m, 3H), 2.05 (br. s., 2H), 1.98 - 1.88 (m, 1H), 1.83 (m, 1H), 1.51 (m, 5H), 1.45 (s, 3H), 1.40 (m, 2H), 1.24 (m, 5H), 1.10 (m, 2H), 1.00 (m, 3H), 0.87 (m, 3H); MS: MS *m/z* 866.8 (M^++1).

Preparation of Compound 6051 and Compound 6052



Compound 6051



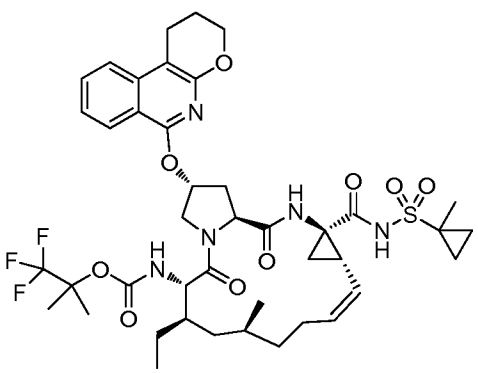
Compound 6052

Compounds 6051 and 6052 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

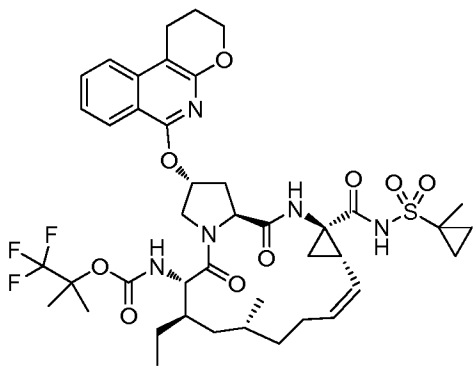
Compound 6051: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 862.8 (M^++1).

Compound 6052: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.01 (br. s., 1H), 8.05 (d, *J*=8.2 Hz, 1H), 7.84 - 7.66 (m, 2H), 7.63 (d, *J*=7.6 Hz, 1H), 7.33 (t, *J*=7.5 Hz, 1H), 5.70 (br. s., 1H), 5.51 (d, *J*=5.8 Hz, 1H), 5.01 (t, *J*=9.5 Hz, 1H), 4.88-4.76 (m, 1H), 4.59 (d, *J*=11.6 Hz, 1H), 4.52 - 4.39 (m, 2H), 4.28 (m, 2H), 3.99 - 3.85 (m, 1H), 3.72 (dd, *J*=10.5, 8.4 Hz, 1H), 2.92 - 2.83 (m, 2H), 2.71 - 2.61 (m, 2H), 2.36 - 2.26 (m, 2H), 2.05 (m, 2H), 1.93 - 1.76 (m, 2H), 1.71 (m, 1H), 1.64 - 1.48 (m, 7H), 1.43 (m, 1H), 1.37 (m, 1H), 1.30 (s, 3H), 1.24 (d, *J*=15.0 Hz, 2H), 1.15 (d, *J*=12.5 Hz, 1H), 1.04 (s, 3H), 0.92 (d, *J*=17.4 Hz, 3H), 0.93 (d, *J*=18.3 Hz, 3H), 0.76 (t, *J*=12.8 Hz, 1H); MS: MS *m/z* 862.8 (M^++1).

Preparation of Compound 6053 and Compound 6054



Compound 6053



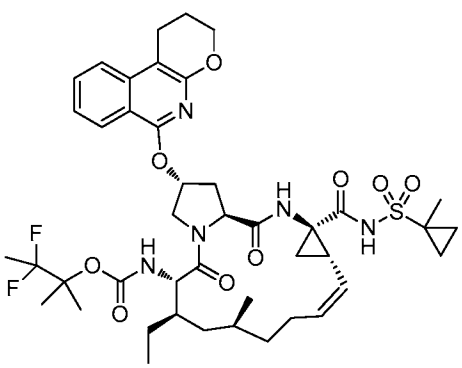
Compound 6054

Compounds 6053 and 6054 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

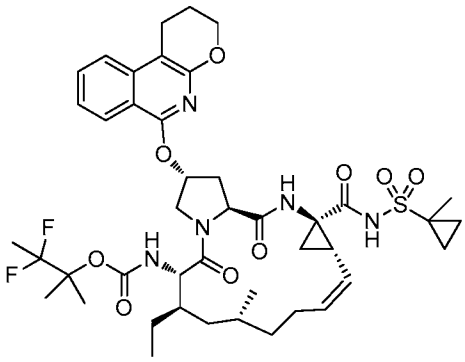
Compound 6053: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 862.6 (M^++1).

Compound 6054: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.11 (br. s., 1H), 8.02 (d, *J*=8.2 Hz, 1H), 7.87 (d, *J*=8.2 Hz, 1H), 7.81 - 7.64 (m, 2H), 7.35 (t, *J*=7.5 Hz, 1H), 5.73 (br. s., 1H), 5.53 (br. s., 1H), 5.06 - 4.94 (m, 1H), 4.58 (d, *J*=11.3 Hz, 1H), 4.54 - 4.44 (m, 1H), 4.29 (t, *J*=5.2 Hz, 2H), 4.00 - 3.78 (m, 2H), 2.88 (d, *J*=2.7 Hz, 2H), 2.75 - 2.61 (m, 2H), 2.35 - 2.23 (m, 2H), 2.11 - 2.01 (m, 2H), 2.01 - 1.79 (m, 2H), 1.62 (br. s., 1H), 1.51 (d, *J*=7.6 Hz, 2H), 1.48 - 1.34 (m, 10H), 1.30 (d, *J*=7.9 Hz, 2H), 1.17 (t, *J*=7.2 Hz, 1H), 1.04 (s, 3H), 0.96 - 0.89 (m, 6H), 0.74 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 862.6 (M^++1).

Preparation of Compound 6055 and Compound 6056



Compound 6055



Compound 6056

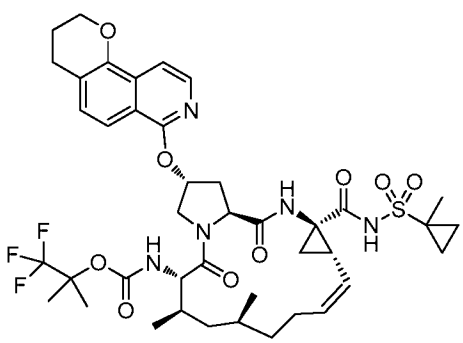
Compounds 6055 and 6056 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6055: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 858.6 (M^++1).

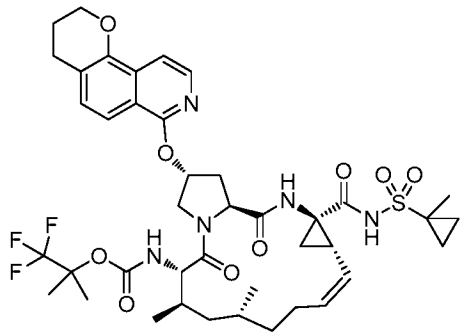
Compound 6056: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.08 (br. s., 1H), 8.02 (d, *J*=8.2 Hz, 1H), 7.78 - 7.58 (m, 3H), 7.34 (t, *J*=7.5 Hz, 1H), 5.73 (br. s., 1H), 5.52 (m, 1H), 5.00 (m, 1H), 4.56 (d, *J*=10.7 Hz, 1H), 4.47 (m, 1H), 4.29 (t, *J*=5.2 Hz, 2H), 3.98 - 3.85 (m, 2H), 2.91 - 2.80 (m, 2H), 2.73 (m, 1H), 2.65 (m, 1H), 2.40 - 2.23 (m, 2H), 2.06 (m, 2H), 1.98 - 1.86 (m, 2H), 1.63 - 1.47 (m, 7H), 1.41 (m, 6H), 1.30 (s, 3H),

1.18 (d, *J*=7.3 Hz, 1H), 0.99 (m, 6H), 0.93 (m, 5H), 0.76 (t, *J*=7.3 Hz, 3H); MS: MS *m/z* 858.6 (M^++1).

Preparation of Compound 6057 and Compound 6058



Compound 6057



Compound 6058

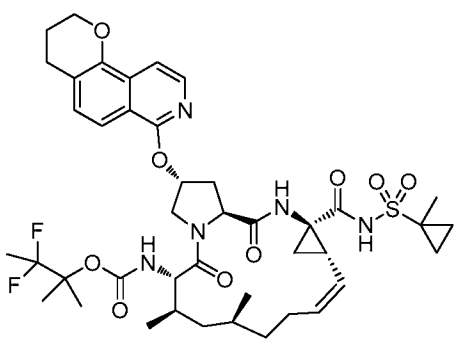
Compounds 6057 and 6058 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6057: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 848.7 (M^++1).

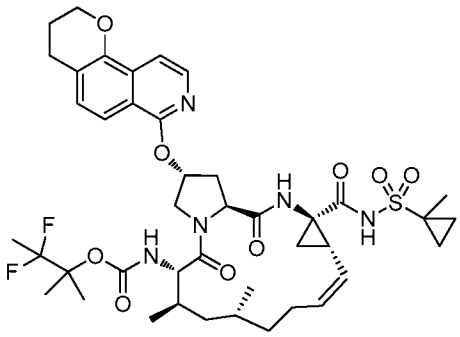
Compound 6058: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.08 (br. s., 1H), 7.96 (d, *J*=6.1 Hz, 1H), 7.76 (d, *J*=7.9 Hz, 1H), 7.55 (d, *J*=8.2 Hz, 1H), 7.42 (d, *J*=6.1 Hz, 1H), 7.22 (d, *J*=8.5 Hz, 1H), 5.81 (br. s., 1H), 5.54 - 5.45 (m, 1H), 5.01 (m, 1H), 4.54 - 4.44 (m, 2H), 4.36 - 4.26 (m, 2H), 3.90 (d, *J*=8.5 Hz, 1H), 3.72 - 3.61 (m, 1H), 2.92 - 2.82 (m, 2H), 2.68 - 2.56 (m, 2H), 2.36 - 2.25 (m, 2H), 2.01 (d, *J*=11.3 Hz, 2H), 1.87 (m, 1H), 1.82 (m, 1H), 1.73 - 1.64 (m, 1H), 1.59

(m, 1H), 1.50 (m, 1H), 1.45 - 1.31 (m, 9H), 1.26 (d, *J*=8.9 Hz, 1H), 1.13 (d, *J*=12.5 Hz, 1H), 1.05 (s, 3H), 0.94 - 0.81 (m, 8H), 0.73 (t, *J*=13.0 Hz, 1H); MS: MS *m/z* 848.7 (M^++1).

Preparation of Compound 6059 and Compound 6060



Compound 6059



Compound 6060

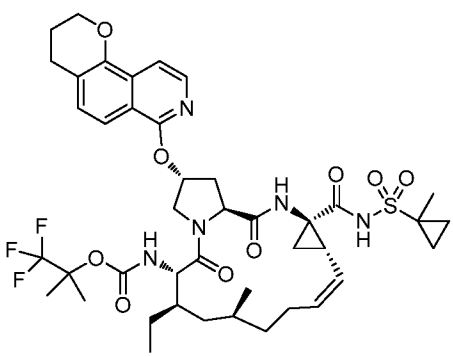
Compounds 6059 and 6060 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6059: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 844.7 (M^++1).

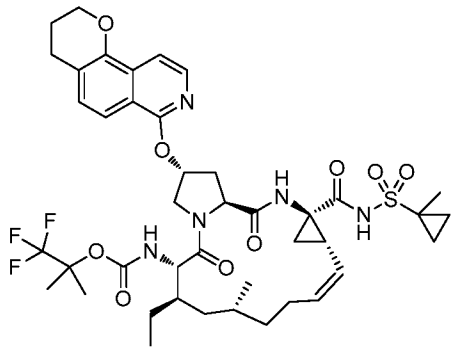
Compound 6060: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.08 (br. s., 1H), 7.95 (d, *J*=5.8 Hz, 1H), 7.54 (t, *J*=9.3 Hz, 2H), 7.42 (d, *J*=5.8 Hz, 1H), 7.21 (d, *J*=8.5 Hz, 1H), 5.80 (br. s., 1H), 5.57 - 5.41 (m, 1H), 5.00 (m, 1H), 4.55 - 4.42 (m, 2H), 4.36 - 4.25 (m, 2H), 3.90 (d, *J*=8.5 Hz, 1H), 3.74 - 3.63 (m, 1H), 2.92 - 2.78 (m, 2H), 2.70 - 2.54 (m, 2H), 2.33 - 2.19 (m, 2H), 2.09 - 1.94 (m,

2H), 1.94 - 1.84 (m, 1H), 1.80 (d, *J*=6.4 Hz, 1H), 1.71 - 1.61 (m, 1H), 1.61 - 1.46 (m, 5H), 1.39 (m, 5H), 1.35 (m, 2H), 1.24 (s, 3H), 1.12 (d, *J*=12.8 Hz, 1H), 0.96 (s, 3H), 0.93 - 0.81 (m, 8H), 0.73 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 844.7 (M^++1).

Preparation of Compound 6061 and Compound 6062



Compound 6061



Compound 6062

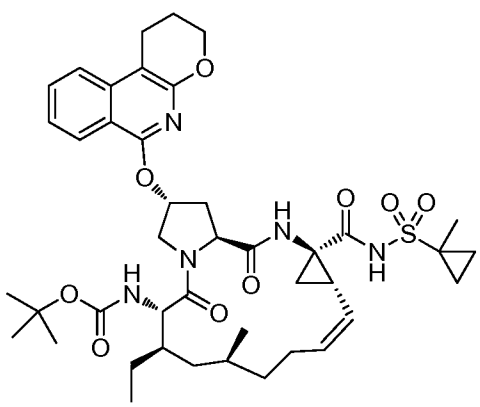
Compounds 6061 and 6062 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6061: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 863.0 (M^++1).

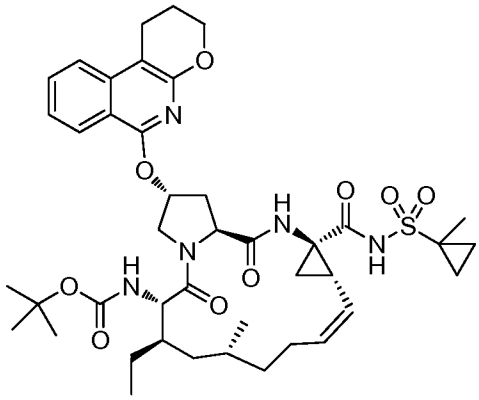
Compound 6062: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.03 (br. s., 1H), 9.13 (br. s., 1H), 7.99 (d, *J*=6.1 Hz, 1H), 7.85 (d, *J*=8.5 Hz, 1H), 7.55 (d, *J*=8.5 Hz, 1H), 7.44 (d, *J*=6.1 Hz, 1H), 7.24 (d, *J*=8.2 Hz, 1H), 5.84 (br. s., 1H), 5.53 (m, 1H), 4.98 (t, *J*=9.5 Hz, 1H), 4.58 - 4.46

(m, 2H), 4.41 - 4.30 (m, 2H), 3.98 - 3.80 (m, 2H), 2.94 - 2.85 (m, 2H), 2.73 - 2.60 (m, 2H), 2.36 - 2.26 (m, 2H), 2.10 - 1.86 (m, 4H), 1.63 (d, *J*=5.8 Hz, 1H), 1.52 (br. s., 3H), 1.49 - 1.39 (m, 6H), 1.39 - 1.23 (m, 6H), 1.23 - 1.11 (m, 2H), 1.05 (m, 2H), 0.95 - 0.89 (m, 5H), 0.73 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 863.0 (M^++1).

Preparation of Compound 6063 and Compound 6064



Compound 6063



Compound 6064

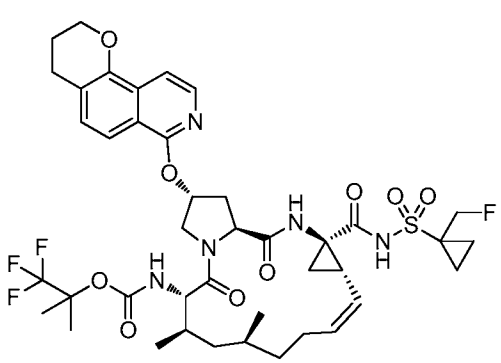
Compounds 6063 and 6064 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6063: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 808.7 (M^++1).

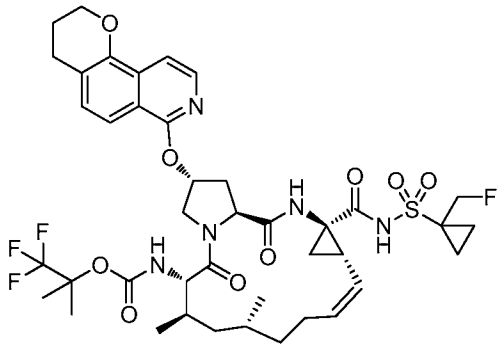
Compound 6064: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.02 (br. s., 1H), 9.06 (br. s., 1H), 8.04 (d, *J*=8.2 Hz, 1H), 7.79 - 7.62 (m, 2H), 7.32 (t, *J*=7.3 Hz, 1H), 7.21 (d, *J*=8.5 Hz, 1H), 5.72 (br. s., 1H), 5.53 (m, 1H), 4.99 (m, 1H),

4.63 (m, 1H), 4.51 - 4.39 (m, 1H), 4.28 (t, *J*=5.0 Hz, 2H), 3.92 (t, *J*=4.1 Hz, 2H), 2.92 - 2.84 (m, 2H), 2.64 (m, 2H), 2.38 (m, 2H), 2.35 - 2.23 (m, 2H), 2.05 (m, 2H), 1.98 - 1.84 (m, 2H), 1.60 (m, 1H), 1.51 (m, 2H), 1.45 (m, 2H), 1.41 (m, 4H), 1.35 (m, 1H), 1.27 (d, *J*=15.6 Hz, 1H), 1.14 (m, 8H), 0.99 (m, 2H), 0.96 - 0.83 (m, 5H), 0.74 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 808.7 (M^++1).

Preparation of Compound 6065 and Compound 6066



Compound 6065



Compound 6066

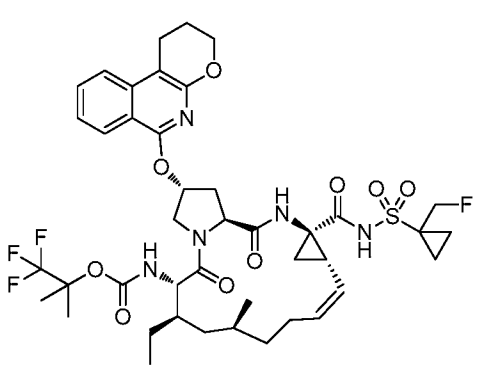
Compounds 6065 and 6066 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6065: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 866.7 (M^++1).

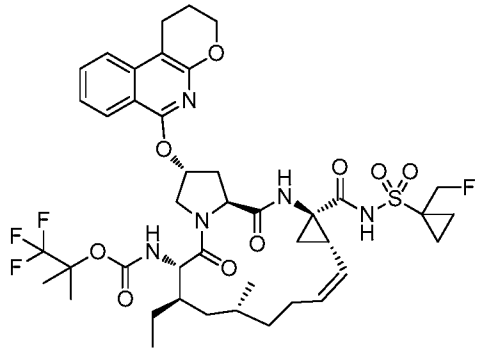
Compound 6066: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate.

^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (br. s., 1H), 9.06 (br. s., 1H), 7.98 (d, *J*=6.1 Hz, 1H), 7.82 (d, *J*=7.0 Hz, 1H), 7.57 (d, *J*=8.5 Hz, 1H), 7.44 (d, *J*=5.8 Hz, 1H), 7.24 (d, *J*=8.5 Hz, 1H), 5.81 (br. s., 1H), 5.52 (m, 1H), 4.99 (m, 1H), 4.60 (d, *J*=10.1 Hz, 1H), 4.55 (m, 1H), 4.49 (m, 2H), 4.39 - 4.30 (m, 2H), 3.97 - 3.86 (m, 1H), 3.74 - 3.62 (m, 1H), 2.93 - 2.86 (m, 2H), 2.65 (m, 1H), 2.40 - 2.26 (m, 3H), 2.09 - 1.97 (m, 2H), 1.92 (m, 1H), 1.85 (m, 2H), 1.70 (m, 1H), 1.53 (m, 3H), 1.37 (m, 5H), 1.25 (m, 2H), 1.19 (m, 1H), 1.12 (s, 3H), 0.97 - 0.84 (m, 6H), 0.74 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 866.7 (M^++1).

Preparation of Compound 6067 and Compound 6068



Compound 6067



Compound 6068

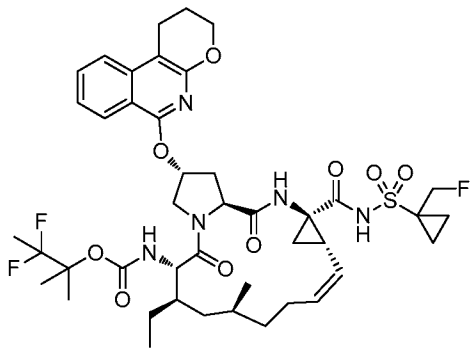
Compounds 6067 and 6068 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6067: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 880.7 (M^++1).

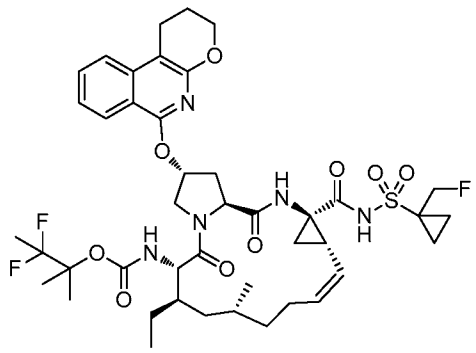
Compound 6068: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-

yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (br. s., 1H), 9.06 (br. s., 1H), 8.02 (d, *J*=7.9 Hz, 1H), 7.84 (d, *J*=8.2 Hz, 1H), 7.78 - 7.64 (m, 2H), 7.33 (t, *J*=7.5 Hz, 1H), 5.70 (br. s., 1H), 5.48 (m, 1H), 5.06 (m, 1H), 4.63 - 4.40 (m, 3H), 4.28 (m, 2H), 3.91 (d, *J*=10.4 Hz, 2H), 2.87 (m, 2H), 2.61 (m, 2H), 2.35 - 2.22 (m, 2H), 2.10 - 2.00 (m, 2H), 1.99 - 1.81 (m, 2H), 1.50 (m, 5H), 1.39-1.17 (m, 11H), 1.08 (s, 3H), 1.03 - 0.87 (m, 4H), 0.73 (t, *J*=7.2 Hz, 3H); MS: MS *m/z* 880.7 (M^++1).

Preparation of Compound 6069 and Compound 6070



Compound 6069



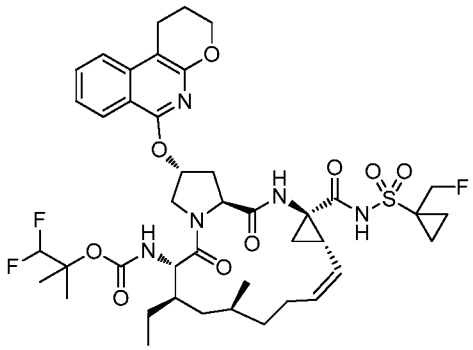
Compound 6070

Compounds 6069 and 6070 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

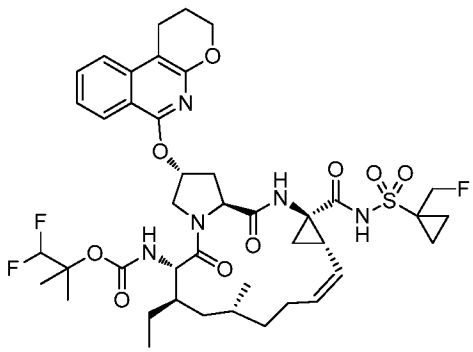
Compound 6069: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 876.9 (M^++1).

Compound 6070: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (br. s., 1H), 9.06 (br. s., 1H), 8.02 (d, *J*=8.2 Hz, 1H), 7.79 - 7.66 (m, 2H), 7.63 (d, *J*=8.5 Hz, 1H), 7.32 (t, *J*=7.6 Hz, 1H), 5.70 (br. s., 1H), 5.48 (m, 1H), 5.05 (m, 1H), 4.63 - 4.39 (m, 3H), 4.28 (t, *J*=4.9 Hz, 2H), 3.91 (d, *J*=9.8 Hz, 2H), 2.86 (m, 2H), 2.61 (m, 2H), 2.29 (t, *J*=10.1 Hz, 2H), 2.05 (m, 2H), 1.92 (m, 2H), 1.65 - 1.46 (m, 8H), 1.43 (m, 4H), 1.31 (m, 5H), 1.24 (m, 1H), 1.18 (m, 2H), 1.02 (s, 3H), 0.93 (d, *J*=6.4 Hz, 3H), 0.75 (t, *J*=7.3 Hz, 3H); MS: MS *m/z* 876.9 (M^++1).

Preparation of Compound 6071 and Compound 6072



Compound 6071



Compound 6072

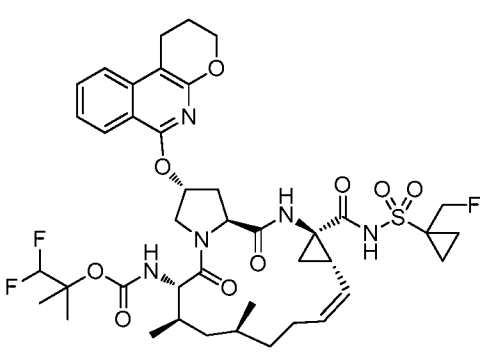
Compounds 6071 and 6072 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6071: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

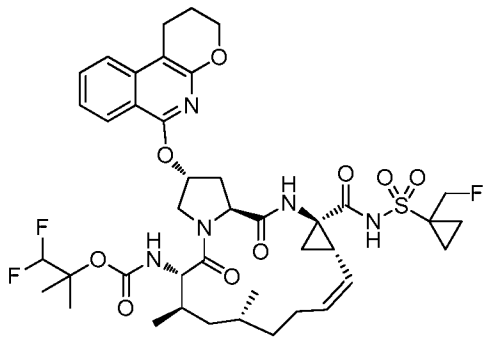
hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 862.8 (M^++1).

Compound 6072: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (br. s., 1H), 9.06 (br. s., 1H), 8.01 (d, *J*=8.2 Hz, 1H), 7.77 - 7.65 (m, 3H), 7.33 (t, *J*=7.6 Hz, 1H), 5.97- 5.68 (m, 2H), 5.49 (m, 1H), 5.01 (m, 1H), 4.83 (m, 1H), 4.73 (rm, 1H), 4.60 (d, *J*=9.5 Hz, 1H), 4.53 - 4.39 (m, 2H), 4.28 (m, 2H), 3.95 - 3.82 (m, 2H), 2.94 - 2.83 (m, 2H), 2.61 (m, 1H), 2.29 (t, *J*=10.1 Hz, 2H), 2.05 (d, *J*=5.8 Hz, 2H), 1.92 (m, 2H), 1.51 (m, 4H), 1.41 (m, 3H), 1.33 (m, 2H), 1.24 (m, 2H), 1.18 (d, *J*=17.4 Hz, 2H), 1.08 (s, 3H), 1.10 (s, 3H), 0.92 (m, 3H), 0.72 (t, *J*=7.5 Hz, 3H); MS: MS *m/z* 862.8 (M^++1).

Preparation of Compound 6073 and Compound 6074



Compound 6073



Compound 6074

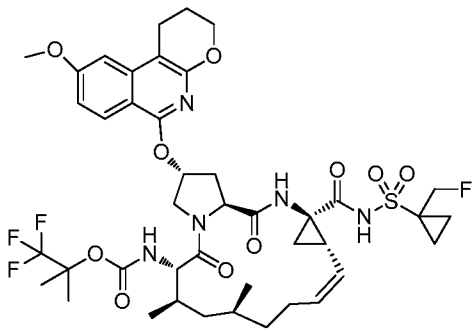
Compounds 6073 and 6074 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6073: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

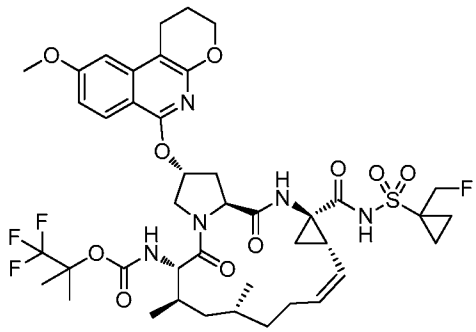
hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 848.7 (M^++1).

Compound 6074: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ11.27 (br. s., 1H), 9.06 (br. s., 1H), 8.02 (d, *J*=7.6 Hz, 1H), 7.77 - 7.66 (m, 2H), 7.62 (d, *J*=7.9 Hz, 1H), 7.32 (t, *J*=7.5 Hz, 1H), 5.90-5.59 (m, 2H), 5.49 (m, 1H), 5.01 (m, 1H), 4.83 (d, *J*=10.4 Hz, 1H), 4.73 (d, *J*=10.7 Hz, 1H), 4.65 - 4.55 (m, 2H), 4.52 - 4.40 (m, 2H), 4.29 - 4.20 (m, 2H), 3.87 (d, *J*=8.9 Hz, 1H), 3.72 - 3.63 (m, 2H), 2.93 - 2.77 (m, 2H), 2.59 (m, 2H), 2.27 (t, *J*=9.8 Hz, 2H), 2.08 - 1.98 (m, 2H), 1.86 (m, 1H), 1.79 (d, *J*=6.7 Hz, 1H), 1.67 (m, 1H), 1.50 (d, *J*=11.9 Hz, 2H), 1.36 (d, *J*=15.0 Hz, 2H), 1.22 (m, 2H), 1.19 - 1.09 (m, 2H), 1.06 (m, 4H), 0.97 - 0.82 (m, 6H), 0.71 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 848.7 (M^++1).

Preparation of Compound 6075 and Compound 6076



Compound 6075



Compound 6076

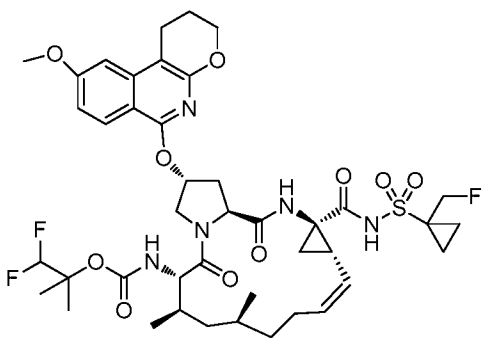
Compounds 6075 and 6076 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6075: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-

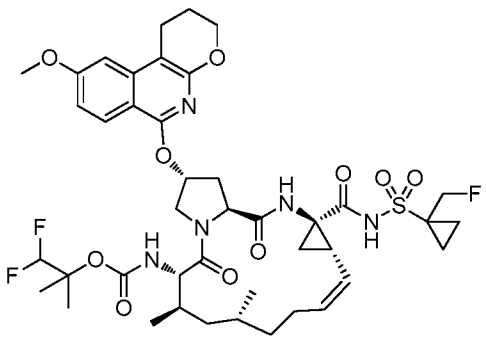
(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 896.8 (M^++1).

Compound 6076: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.99 (d, *J*=9.0 Hz, 1H), 6.99 (d, *J*=2.3 Hz, 1H), 6.89 (dd, *J*=9.2, 2.4 Hz, 1H), 5.73 (br. s., 1H), 5.56 (td, *J*=10.2, 5.5 Hz, 1H), 5.15 (t, *J*=9.8 Hz, 1H), 4.79 - 4.49 (m, 4H), 4.34 (t, *J*=5.0 Hz, 2H), 4.01 - 3.89 (m, 4H), 3.81 (d, *J*=10.8 Hz, 1H), 2.92 - 2.82 (m, 2H), 2.74 - 2.54 (m, 2H), 2.47 - 2.32 (m, 2H), 2.14 (dd, *J*=6.1, 3.9 Hz, 2H), 1.95 (s, 2H), 1.90 - 1.74 (m, 2H), 1.71 - 1.51 (m, 4H), 1.49 - 1.33 (m, 5H), 1.32 - 1.08 (m, 4H), 1.03 - 0.95 (m, 7H), 0.80 (t, *J*=11.3 Hz, 1H); MS: MS *m/z* 896.8 (M^++1).

Preparation of Compound 6077 and Compound 6078



Compound 6077



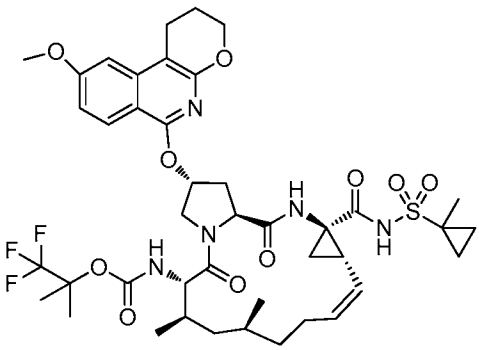
Compound 6078

Compounds 6077 and 6078 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

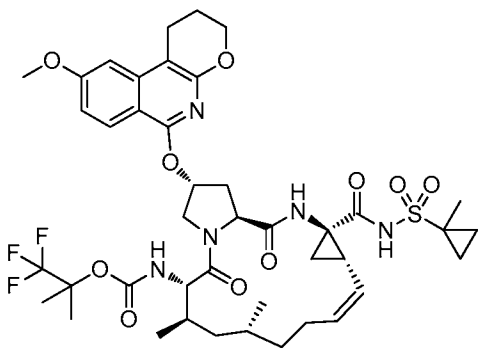
Compound 6077: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 878.9 (M^++1).

Compound 6078: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.98 (d, *J*=9.0 Hz, 1H), 6.98 (d, *J*=2.3 Hz, 1H), 6.89 (dd, *J*=9.0, 2.3 Hz, 1H), 5.76 - 5.65 (m, 1H), 5.61 - 5.48 (m, 2H), 5.18 (t, *J*=9.8 Hz, 1H), 4.76 (dd, *J*=15.7, 11.2 Hz, 1H), 4.70 - 4.48 (m, 2H), 4.34 (t, *J*=5.1 Hz, 2H), 4.00 - 3.87 (m, 5H), 3.77 (d, *J*=10.8 Hz, 1H), 2.92 - 2.81 (m, 2H), 2.74 - 2.54 (m, 2H), 2.41 (ddd, *J*=13.9, 10.1, 4.1 Hz, 2H), 2.22 - 2.09 (m, 2H), 1.86 - 1.76 (m, 2H), 1.72 - 1.48 (m, 4H), 1.48 - 1.37 (m, 2H), 1.33 - 1.12 (m, 4H), 1.10 - 0.91 (m, 12H), 0.79 (t, *J*=11.7 Hz, 1H); MS: MS *m/z* 878.9 (M^++1).

Preparation of Compound 6079 and Compound 6080



Compound 6079



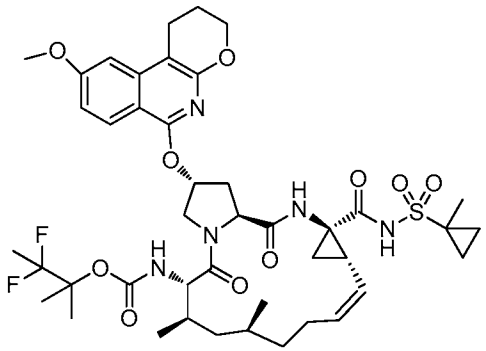
Compound 6080

Compounds 6079 and 6080 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

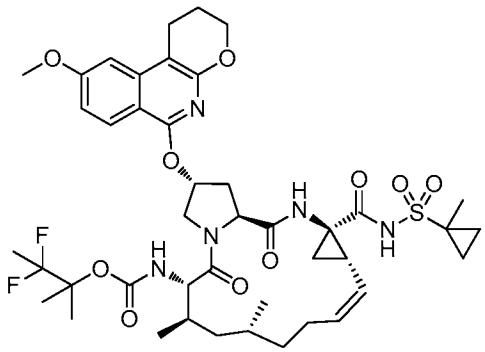
Compound 6079: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 878.8 (M^++1).

Compound 6080: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.99 (d, *J*=9.0 Hz, 1H), 6.99 (d, *J*=2.3 Hz, 1H), 6.89 (dd, *J*=9.0, 2.3 Hz, 1H), 5.81 - 5.70 (m, 1H), 5.59 (td, *J*=10.2, 5.8 Hz, 1H), 5.02 (t, *J*=9.8 Hz, 1H), 4.75 (d, *J*=11.0 Hz, 1H), 4.67 - 4.56 (m, 1H), 4.34 (t, *J*=5.1 Hz, 2H), 4.03 - 3.88 (m, 4H), 3.81 (d, *J*=10.8 Hz, 1H), 2.87 (d, *J*=5.0 Hz, 2H), 2.75 - 2.61 (m, 2H), 2.49 - 2.34 (m, 2H), 2.14 (dd, *J*=6.0, 3.8 Hz, 2H), 1.99 - 1.71 (m, 4H), 1.68 - 1.60 (m, 2H), 1.58 - 1.33 (m, 9H), 1.33 - 1.13 (m, 2H), 1.04 - 0.92 (m, 8H), 0.87 (s, 3H); MS: MS *m/z* 878.8 (M^++1).

Preparation of Compound 6081 and Compound 6082



Compound 6081



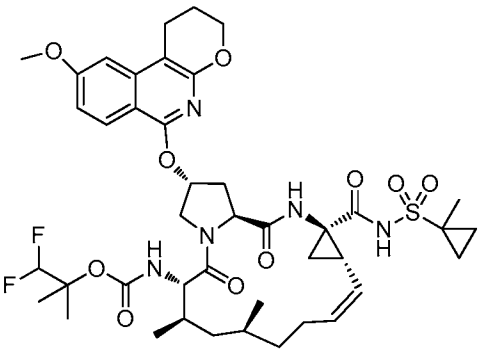
Compound 6082

Compounds 6081 and 6082 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

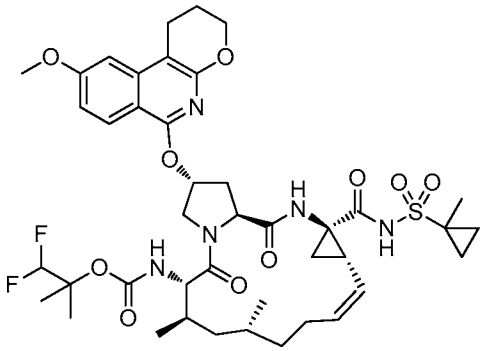
Compound 6081: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 874.9 (M^++1).

Compound 6082: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.99 (d, *J*=9.0 Hz, 1H), 6.98 (d, *J*=2.5 Hz, 1H), 6.88 (dd, *J*=9.0, 2.3 Hz, 1H), 5.75 (br. s., 1H), 5.59 (td, *J*=10.2, 5.6 Hz, 1H), 5.02 (t, *J*=9.5 Hz, 1H), 4.71 (d, *J*=11.5 Hz, 1H), 4.66 - 4.56 (m, 1H), 4.39 - 4.28 (m, 2H), 4.06 - 3.89 (m, 4H), 3.88 - 3.74 (m, 1H), 2.93 - 2.80 (m, 2H), 2.69 (t, *J*=8.8 Hz, 2H), 2.50 - 2.29 (m, 2H), 2.20 - 2.06 (m, 2H), 1.99 - 1.69 (m, 4H), 1.69 - 1.48 (m, 8H), 1.48 - 1.35 (m, 4H), 1.35 - 1.13 (m, 5H), 1.05 - 0.75 (m, 10H); MS: MS *m/z* 874.9 (M^++1).

Preparation of Compound 6083 and Compound 6084



Compound 6083



Compound 6084

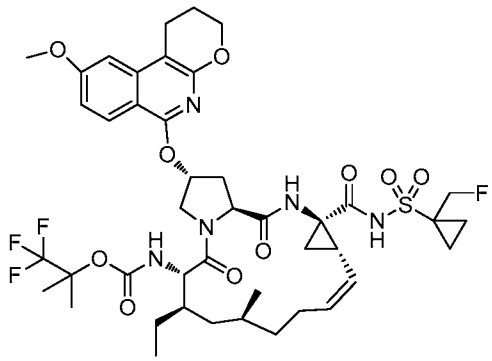
Compounds 6083 and 6084 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6083: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 860.9 (M^++1).

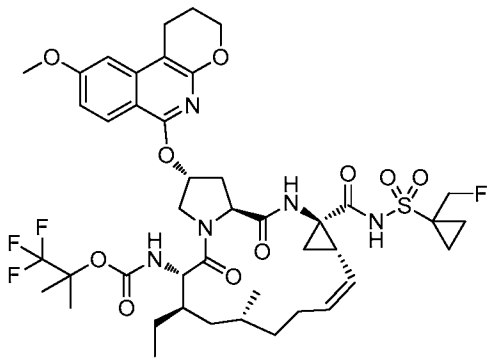
Compound 6084: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.98 (d, *J*=9.0 Hz, 1H), 6.98 (d, *J*=2.3 Hz, 1H), 6.89 (dd, *J*=9.0, 2.3 Hz, 1H), 5.76 - 5.70 (m, 1H), 5.63 - 5.54 (m, 1H), 5.05 (t, *J*=9.4 Hz, 1H), 4.80 (d, *J*=11.5 Hz, 1H), 4.69 - 4.57 (m, 1H), 4.34 (t, *J*=5.1 Hz, 2H), 3.97 - 3.90 (m, 4H), 3.77 (d, *J*=10.8 Hz, 1H), 2.89 - 2.82 (m, 2H), 2.75 - 2.63 (m, 2H), 2.46 - 2.29 (m, 2H), 2.14 (d, *J*=3.3 Hz, 2H), 1.99 - 1.88 (m, 1H), 1.88 - 1.72 (m, 3H), 1.66 - 1.48 (m, 5H), 1.48 - 1.38 (m,

3H), 1.33 - 1.15 (m, 3H), 1.05 (s, 3H), 1.08 (m, 2H), 0.98 (t, *J*=7.2 Hz, 6H), 0.90 - 0.75 (m, 3H); MS: MS *m/z* 860.9 (M^++1).

Preparation of Compound 6085 and Compound 6086



Compound 6085



Compound 6086

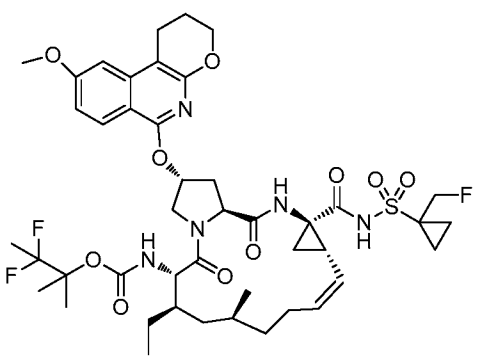
Compounds 6085 and 6086 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6085: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 911.1 (M^++1).

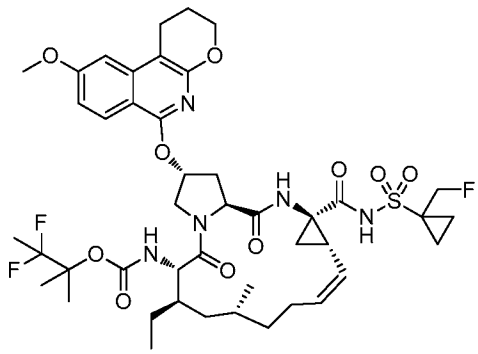
Compound 6086: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400MHz, METHANOL-d_4) δ 8.01 (d, *J*=9.3 Hz, 1H), 6.99 (d, *J*=2.3 Hz, 1H), 6.90 (dd, *J*=9.0, 2.3 Hz, 1H), 5.75 (br. s., 1H), 5.67 (d, *J*=8.8 Hz, 1H), 5.16 (m, 1H), 4.69 - 4.47 (m, 2H), 4.40 - 4.27 (m,

2H), 4.06 (d, *J*=11.3 Hz, 1H), 3.93 (s, 3H), 2.91 - 2.83 (m, 2H), 2.67 (dd, *J*=13.8, 6.8 Hz, 1H), 2.56 - 2.38 (m, 2H), 2.33 (m, 1H), 2.18 - 2.12 (m, 2H), 2.07 - 1.91 (m, 1H), 1.87 (m, 1H), 1.66 (m, 2H), 1.63 - 1.52 (m, 4H), 1.52 - 1.39 (m, 6H), 1.31 (dt, *J*=9.4, 4.6 Hz, 4H), 1.18 (m, 4H), 1.04 - 0.95 (m, 4H), 0.90 (m, *J*=6.8 Hz, 4H); MS: MS *m/z* 911.1 (M^++1).

Preparation of Compound 6087 and Compound 6088



Compound 6087



Compound 6088

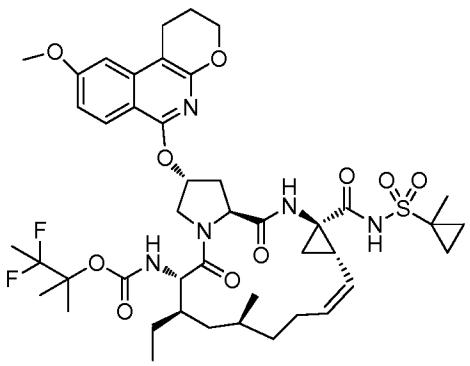
Compounds 6087 and 6088 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6087: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 907.1 (M^++1).

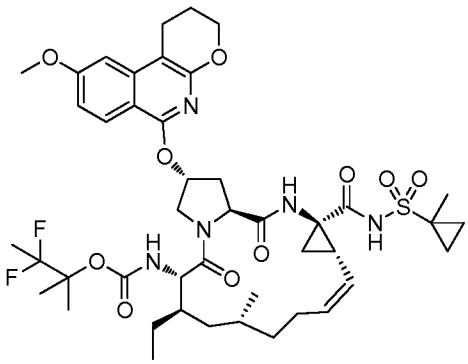
Compound 6088: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 907.1 (M^++1).

Preparation of Compound 6089 and Compound 6090



Compound 6089



Compound 6090

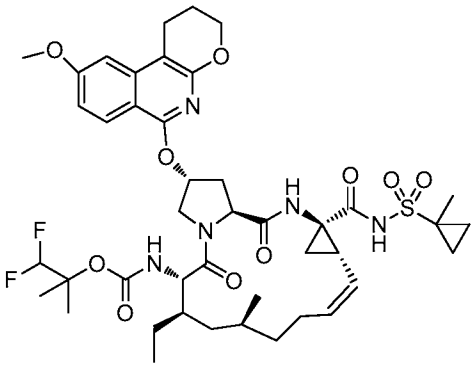
Compounds 6089 and 6090 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6089: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 889.1 (M^++1).

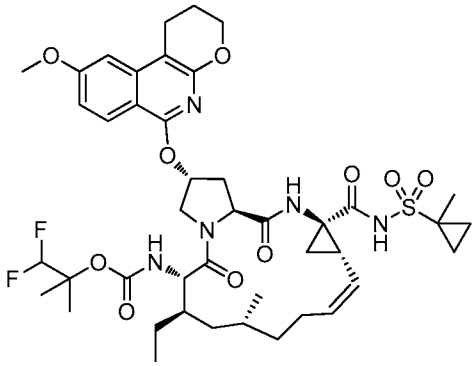
Compound 6090: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.99 (d, *J*=9.0 Hz, 1H), 6.99 (d, *J*=2.5 Hz, 1H), 6.89 (dd, *J*=9.0, 2.3 Hz, 1H), 5.77 (br. s., 1H), 5.58 (m, 1H), 4.73 (d, *J*=11.8 Hz, 1H), 4.65 - 4.55 (m, 2H), 4.39 - 4.30 (m,

2H), 4.07 (d, *J*=11.3 Hz, 1H), 3.98 (m, 1H), 3.93 (s, 3H), 2.87 (d, *J*=3.8 Hz, 2H), 2.70 (dd, *J*=13.4, 7.2 Hz, 2H), 2.48 - 2.34 (m, 2H), 2.19 - 2.09 (m, 2H), 2.02 - 1.85 (m, 2H), 1.80 - 1.67 (m, 1H), 1.64 - 1.35 (m, 14H), 1.35 - 1.23 (m, 5H), 1.07 - 0.90 (m, 6H), 0.83 (m, 5H); MS: MS *m/z* 889.1 (M^++1).

Preparation of Compound 6091 and Compound 6092



Compound 6091



Compound 6092

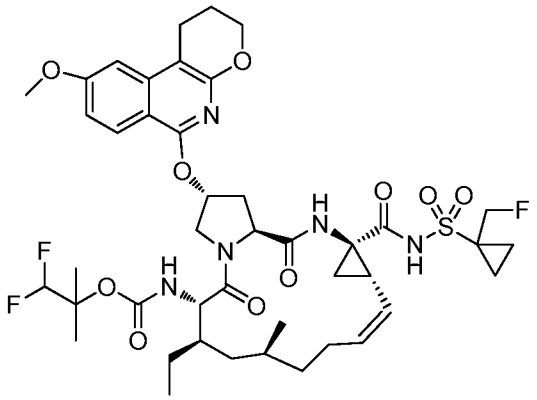
Compounds 6091 and 6092 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6091: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 875.0 (M^++1).

Compound 6092: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400MHz, METHANOL-d_4) δ

7.98 (d, *J*=9.0 Hz, 1H), 6.99 (s, 1H), 6.90 (dd, *J*=9.0, 2.3 Hz, 1H), 5.81 - 5.55 (m, 4H), 4.81 (d, *J*=11.5 Hz, 1H), 4.68 - 4.56 (m, 2H), 4.35 (t, *J*=4.6 Hz, 2H), 4.05 - 3.86 (m, 6H), 2.96 - 2.83 (m, 2H), 2.76 - 2.63 (m, 2H), 2.40 (ddd, *J*=13.6, 10.0, 4.0 Hz, 2H), 2.20 - 2.10 (m, 2H), 2.00 - 1.88 (m, 2H), 1.77 - 1.70 (m, 1H), 1.66 - 1.47 (m, 1H), 1.47 - 1.34 (m, 4H), 1.32 - 1.18 (m, 2H), 1.06 (m, 4H), 1.08 (m, 4H), 0.99 (m, 4H), 0.89 - 0.76 (m, 6H); MS: MS *m/z* 875.0 (M^++1).

Preparation of Compound 6093

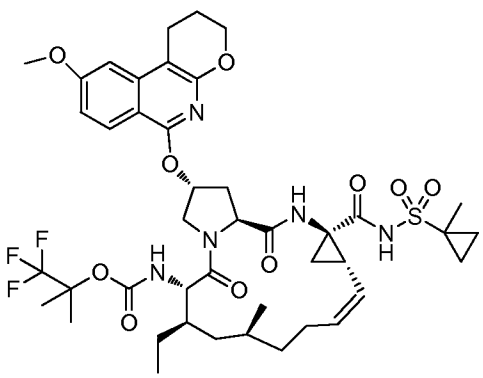


Compound 6093

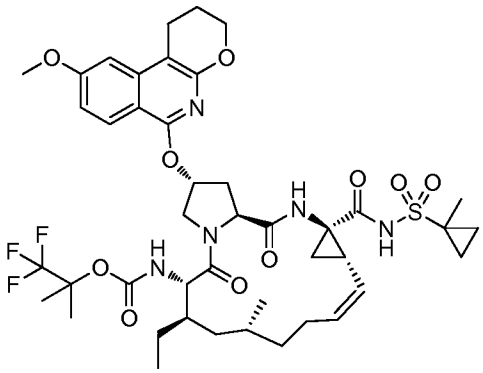
Compounds 6093 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6093: 1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 893.0 (M^++1).

Preparation of Compound 6094 and Compound 6095



Compound 6094



Compound 6095

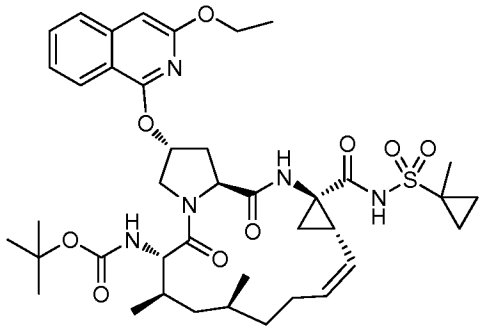
Compounds 6094 and 6095 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6094: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 892.8 (M^++1).

Compound 6095: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.98 (d, *J*=9.0 Hz, 1H), 6.99 (d, *J*=2.3 Hz, 1H), 6.89 (dd, *J*=9.2, 2.4 Hz, 1H), 5.76 (br. s., 1H), 5.63 - 5.51 (m, 1H), 5.08 (br. s., 1H), 4.75 (d, *J*=10.5 Hz, 1H), 4.66 - 4.52 (m, 1H), 4.35 (t, *J*=5.0 Hz, 2H), 4.09 - 3.86 (m, 5H), 2.91 - 2.82 (m, 2H), 2.75 - 2.62 (m, 2H), 2.40 (ddd, *J*=13.8, 9.9, 4.1 Hz, 2H), 2.19 - 2.11 (m, 2H), 2.02 - 1.89 (m, 2H), 1.74 (dd, *J*=8.3, 5.5 Hz, 1H), 1.65 - 1.46 (m, 8H), 1.45 - 1.35 (m, 5H), 1.33 - 1.17 (m,

2H), 1.10 (t, *J*=12.5 Hz, 1H), 0.99 (t, *J*=3.3 Hz, 6H), 0.88 - 0.77 (m, 5H); MS: MS *m/z* 892.8 (M^++1).

Preparation of Compound 6096

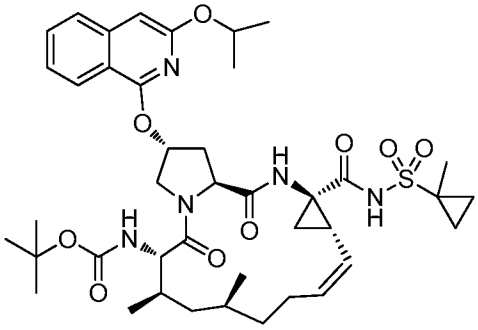


Compound 6096

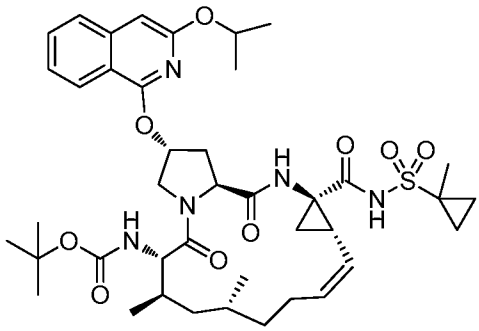
Compounds 6096 was prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6096: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 782.5 (M^++1).

Preparation of Compound 6097 and Compound 6098



Compound 6097



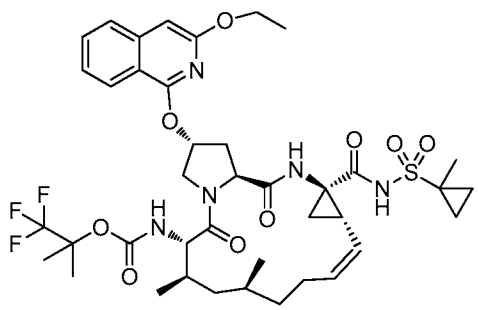
Compound 6098

Compounds 6097 and 6098 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

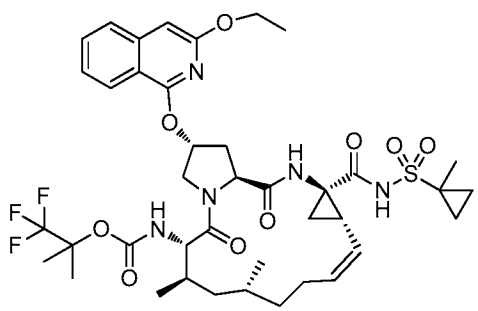
Compound 6097: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 796.4 (M^++1).

Compound 6098: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400MHz, METHANOL-d_4) δ 8.06 (d, *J*=8.2 Hz, 1H), 7.65 - 7.57 (d, *J*=8.2 Hz, 1H), 7.56 - 7.49 (d, *J*=8.2 Hz, 1H), 7.22 (t, *J*=7.2 Hz, 1H), 6.70 (d, *J*=7.9 Hz, 1H), 6.56 (s, 1H), 5.87 (br. s., 1H), 5.53 (td, *J*=10.1, 5.6 Hz, 1H), 5.29 - 5.19 (m, 1H), 5.01 (t, *J*=10.0 Hz, 1H), 4.77 (d, *J*=11.3 Hz, 1H), 4.62 (dd, *J*=9.8, 7.0 Hz, 1H), 4.07 (dd, *J*=11.5, 3.5 Hz, 1H), 3.94 - 3.84 (m, 1H), 2.83 - 2.64 (m, 2H), 2.53 - 2.36 (m, 2H), 1.98 - 1.68 (m, 4H), 1.68 - 1.59 (m, 3H), 1.50 (s, 3H), 1.40 (dd, *J*=6.0, 4.0 Hz, 8H), 1.16 (s, 9H), 0.99 (dd, *J*=6.7, 1.9 Hz, 6H), 0.90 - 0.76 (m, 3H); MS: MS *m/z* 796.4 (M^++1).

Preparation of Compound 6099 and Compound 6100



Compound 6099



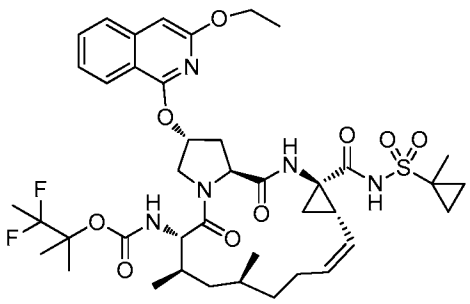
Compound 6100

Compounds 6099 and 6100 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

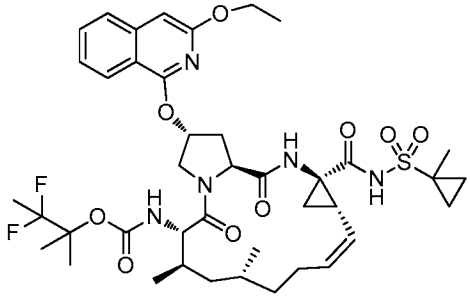
Compound 6099: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 836.5 (M^++1).

Compound 6100: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.13 (br. s., 1H), 8.00 (d, *J*=8.2 Hz, 1H), 7.85 (d, *J*=7.9 Hz, 1H), 7.73 (d, *J*=8.2 Hz, 1H), 7.63 (t, *J*=7.6 Hz, 1H), 7.31 (t, *J*=7.5 Hz, 1H), 6.69 (s, 1H), 5.81 (br. s., 1H), 5.54 (d, *J*=6.1 Hz, 1H), 4.98 (t, *J*=9.8 Hz, 1H), 4.63 - 4.50 (m, 2H), 4.32 - 4.24 (m, 2H), 3.99 - 3.88 (m, 1H), 3.72 (dd, *J*=10.7, 8.2 Hz, 1H), 2.75 - 2.59 (m, 2H), 2.37 - 2.24 (m, 2H), 1.96 - 1.79 (m, 2H), 1.73 - 1.66 (m, 1H), 1.62 (m, 1H), 1.57 - 1.50 (m, 1H), 1.48 - 1.33 (m, 11H), 1.29 (m, 1H), 1.14 (m, 1H), 1.09 (s, 3H), 0.92 (dd, *J*=19.4, 6.6 Hz, 9H), 0.77 (t, *J*=12.8 Hz, 1H); MS: MS *m/z* 836.5 (M^++1).

Preparation of Compound 6101 and Compound 6102



Compound 6101



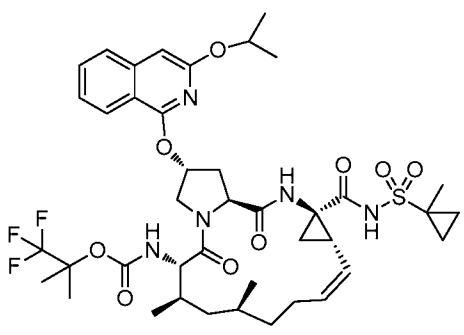
Compound 6102

Compounds 6101 and 6102 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

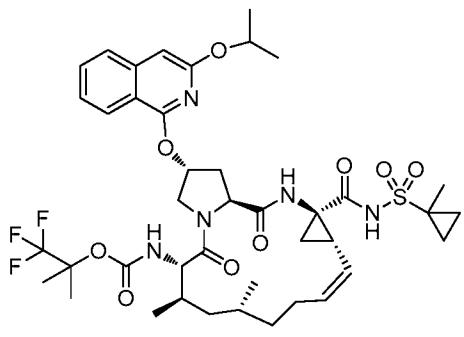
Compound 6101: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 832.5 (M^++1).

Compound 6102: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.05 (br. s., 1H), 9.10 (br. s., 1H), 8.00 (d, *J*=8.5 Hz, 1H), 7.73 (d, *J*=8.2 Hz, 1H), 7.67 - 7.59 (m, 2H), 7.30 (t, *J*=7.5 Hz, 1H), 6.69 (s, 1H), 5.81 (br. s., 1H), 5.54 (m, 1H), 4.99 (t, *J*=9.0 Hz, 1H), 4.61 - 4.47 (m, 2H), 4.35 - 4.20 (m, 2H), 3.98 - 3.88 (m, 1H), 3.77 - 3.67 (m, 1H), 2.76 - 2.68 (m, 1H), 2.65 (m, 1H), 2.39 - 2.25 (m, 2H), 1.98 - 1.88 (m, 2H), 1.84 (d, *J*=6.4 Hz, 1H), 1.70 (m, 2H), 1.57 (m, 6H), 1.49 - 1.33 (m, 10H), 1.27 (s, 4H), 1.15 (m, 1H), 1.02 (s, 3H), 0.92 (dd, *J*=16.6, 6.6 Hz, 6H), 0.77 (t, *J*=12.1 Hz, 1H); MS: MS *m/z* 832.5 (M^++1).

Preparation of Compound 6103 and Compound 6104



Compound 6103



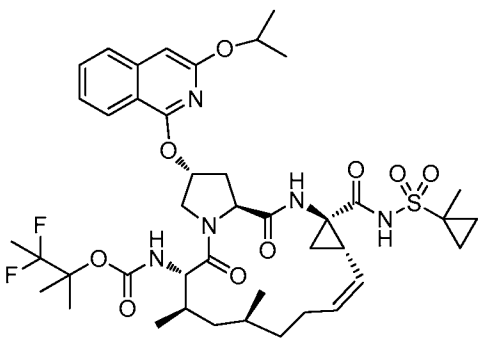
Compound 6104

Compounds 6103 and 6104 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

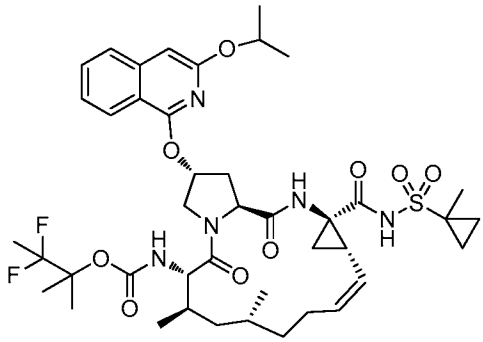
Compound 6103: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 850.1 (M^++1).

Compound 6104: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.13 (br. s., 1H), 7.99 (d, *J*=8.2 Hz, 1H), 7.86 (d, *J*=7.6 Hz, 1H), 7.71 (d, *J*=8.2 Hz, 1H), 7.61 (t, *J*=7.6 Hz, 1H), 7.29 (t, *J*=7.5 Hz, 1H), 6.67 (s, 1H), 5.80 (br. s., 1H), 5.54 (d, *J*=5.8 Hz, 1H), 5.13 (dt, *J*=12.2, 6.1 Hz, 1H), 4.98 (t, *J*=9.9 Hz, 1H), 4.66 - 4.43 (m, 2H), 3.95 (dd, *J*=11.3, 3.4 Hz, 1H), 3.72 (dd, *J*=10.7, 8.2 Hz, 1H), 2.75 - 2.60 (m, 2H), 2.40 - 2.26 (m, 2H), 1.96 - 1.79 (m, 2H), 1.69 (d, *J*=5.5 Hz, 1H), 1.62 (m, 1H), 1.53 (br. s., 1H), 1.49 - 1.39 (m, 4H), 1.36 (d, *J*=5.8 Hz, 10H), 1.33 - 1.20 (m, 2H), 1.14 (d, *J*=13.1 Hz, 1H), 1.08 (s, 3H), 0.98 - 0.85 (m, 8H), 0.76 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 850.1 (M^++1).

Preparation of Compound 6105 and Compound 6106



Compound 6105



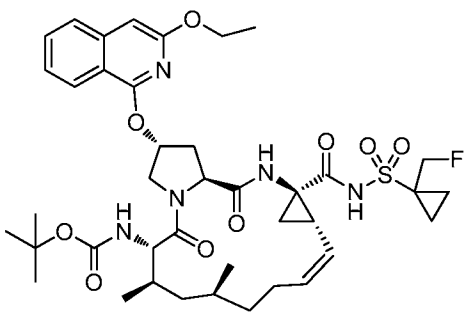
Compound 6106

Compounds 6105 and 6106 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

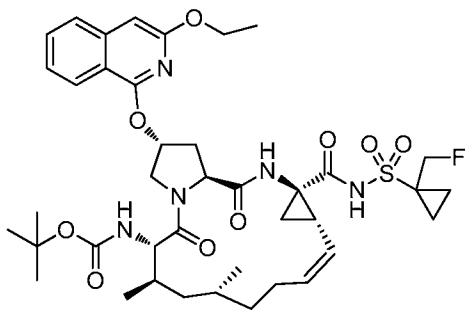
Compound 6105: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 846.1 (M^++1).

Compound 6106: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.10 (s, 1H), 8.00 (d, *J*=8.2 Hz, 1H), 7.71 (d, *J*=8.2 Hz, 1H), 7.68 - 7.53 (m, 2H), 7.28 (t, *J*=7.6 Hz, 1H), 6.67 (s, 1H), 5.80 (br. s., 1H), 5.58 - 5.38 (m, 1H), 5.20 - 5.08 (m, 1H), 4.98 (t, *J*=9.9 Hz, 1H), 4.59 (d, *J*=11.0 Hz, 1H), 4.56 - 4.45 (m, 1H), 3.96 (dd, *J*=11.3, 3.4 Hz, 1H), 3.79 - 3.67 (m, 1H), 2.78 - 2.59 (m, 2H), 2.40 - 2.27 (m, 2H), 1.98 - 1.78 (m, 2H), 1.70 (dd, *J*=13.1, 7.0 Hz, 2H), 1.65 - 1.49 (m, 6H), 1.42 (m, 5H), 1.36 (m, 7H), 1.28 (s, 3H), 1.15 (d, *J*=8.2 Hz, 1H), 1.02 (s, 3H), 0.92 (dd, *J*=18.0, 6.4 Hz, 7H), 0.77 (t, *J*=12.2 Hz, 1H); MS: MS *m/z* 846.1 (M^++1).

Preparation of Compound 6107 and Compound 6108



Compound 6107



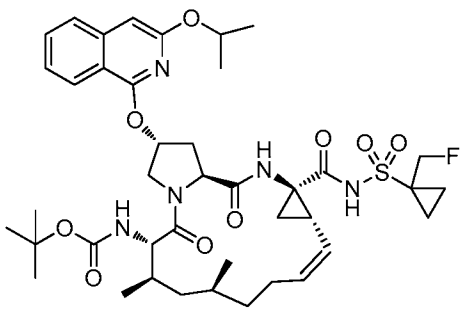
Compound 6108

Compounds 6107 and 6108 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

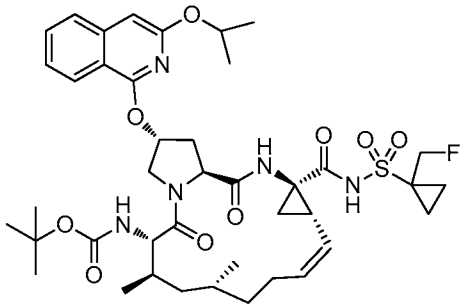
Compound 6107: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 800.5 (M^++1).

Compound 6108: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, METHANOL-d_4) δ 8.07 (d, *J*=8.2 Hz, 1H), 7.63 (d, *J*=8.2 Hz, 1H), 7.55 (t, *J*=7.6 Hz, 1H), 7.24 (t, *J*=7.5 Hz, 1H), 6.68 (d, *J*=8.5 Hz, 1H), 6.59 (s, 1H), 5.87 (br. s., 1H), 5.54 (td, *J*=10.1, 5.8 Hz, 1H), 5.13 - 5.03 (m, 1H), 4.79 - 4.71 (m, 1H), 4.65 - 4.50 (m, 2H), 4.37 (tt, *J*=7.0, 3.5 Hz, 2H), 4.07 (dd, *J*=11.6, 3.4 Hz, 1H), 3.95 - 3.84 (m, 1H), 2.75 (dd, *J*=13.7, 7.0 Hz, 1H), 2.65 (q, *J*=9.1 Hz, 1H), 2.52 - 2.32 (m, 2H), 1.98 - 1.74 (m, 4H), 1.73 - 1.59 (m, 3H), 1.54 (dd, *J*=9.5, 5.2 Hz, 1H), 1.49 - 1.37 (m, 5H), 1.27 - 1.14 (m, 10H), 1.11 (m, 1H), 0.99 (d, *J*=6.7 Hz, 3H), 1.00 (d, *J*=7.0 Hz, 3H), 0.90 - 0.68 (m, 1H); MS: MS *m/z* 800.5 (M^++1).

Preparation of Compound 6109 and Compound 6110



Compound 6109



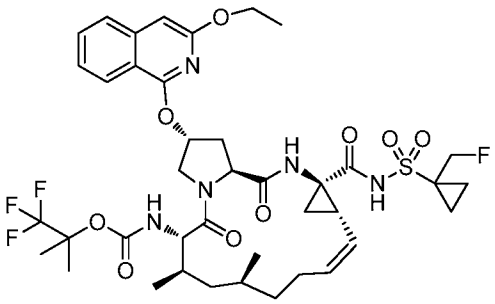
Compound 6110

Compounds 6109 and 6110 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

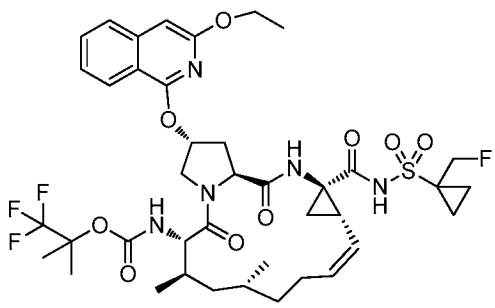
Compound 6109: tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 814.6 (M^++1).

Compound 6110: tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (400MHz, METHANOL-d_4) δ 8.06 (d, *J*=8.5 Hz, 1H), 7.64 - 7.45 (m, 2H), 7.27 - 7.16 (m, 1H), 6.56 (s, 1H), 5.86 (br. s., 1H), 5.51 (td, *J*=10.0, 5.6 Hz, 1H), 5.32 - 5.08 (m, 2H), 4.75 - 4.46 (m, 4H), 4.08 (dd, *J*=11.5, 3.5 Hz, 1H), 3.90 (d, *J*=10.8 Hz, 1H), 2.74 (dd, *J*=13.8, 7.3 Hz, 1H), 2.60 (q, *J*=9.0 Hz, 1H), 2.51 - 2.28 (m, 2H), 2.02 - 1.89 (m, 3H), 1.89 - 1.74 (m, 2H), 1.72 - 1.51 (m, 4H), 1.48 - 1.34 (m, 8H), 1.28 - 1.06 (m, 10H), 0.99 (t, *J*=6.9 Hz, 6H), 0.85 - 0.74 (m, 1H); MS: MS *m/z* 814.6 (M^++1).

Preparation of Compound 6111 and Compound 6112



Compound 6111



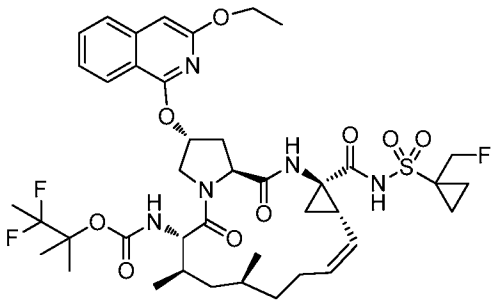
Compound 6112

Compounds 6111 and 6112 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

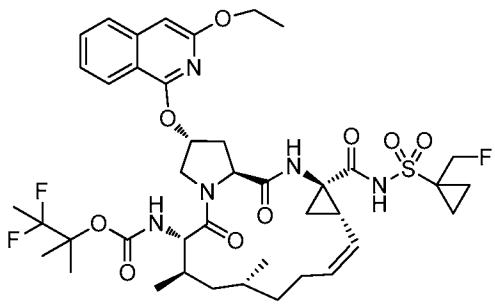
Compound 6111: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 854.5 (M^++1).

Compound 6112: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (s, 1H), 9.04 (s, 1H), 8.01 (d, *J*=8.2 Hz, 1H), 7.85 (d, *J*=7.9 Hz, 1H), 7.74 (d, *J*=8.2 Hz, 1H), 7.63 (t, *J*=7.8 Hz, 1H), 7.31 (t, *J*=7.6 Hz, 1H), 6.69 (s, 1H), 5.80 (br. s., 1H), 5.58 - 5.40 (m, 1H), 5.01 (t, *J*=9.9 Hz, 1H), 4.59 (t, *J*=11.4 Hz, 1H), 4.50 (dd, *J*=7.5, 3.8 Hz, 1H), 4.37 - 4.22 (m, 2H), 3.99 - 3.89 (m, 1H), 3.72 (dd, *J*=10.8, 8.1 Hz, 1H), 2.66 (d, *J*=9.2 Hz, 2H), 2.40 - 2.24 (m, 2H), 1.99 - 1.78 (m, 2H), 1.70 (dd, *J*=12.4, 7.2 Hz, 2H), 1.59 - 1.48 (m, 4H), 1.46 - 1.32 (m, 8H), 1.30 - 1.19 (m, 4H), 1.12 (s, 3H), 0.99 - 0.85 (m, 6H), 0.76 (t, *J*=12.4 Hz, 1H); MS: MS *m/z* 854.5 (M^++1).

Preparation of Compound 6113 and Compound 6114



Compound 6113



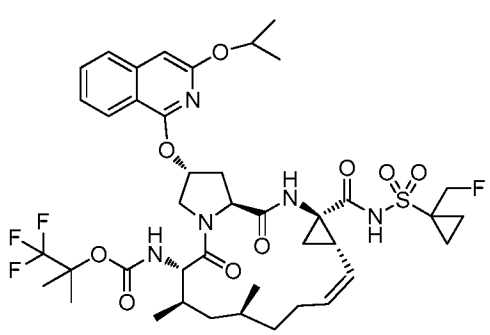
Compound 6114

Compounds 6113 and 6114 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

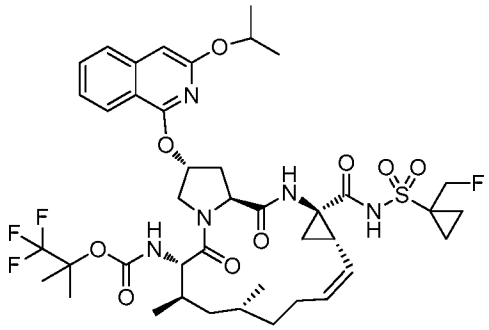
Compound 6113: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 850.6 (M^++1).

Compound 6114: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.27 (s, 1H), 9.02 (s, 1H), 8.01 (d, *J*=7.9 Hz, 1H), 7.73 (d, *J*=8.2 Hz, 1H), 7.66 - 7.58 (m, 2H), 7.30 (t, *J*=7.6 Hz, 1H), 6.69 (s, 1H), 5.80 (br. s., 1H), 5.60 - 5.45 (m, 1H), 5.01 (t, *J*=9.8 Hz, 1H), 4.63 - 4.54 (m, 1H), 4.54 - 4.45 (m, 1H), 4.34 - 4.25 (m, 2H), 4.01 - 3.90 (m, 1H), 3.74 (dd, *J*=10.7, 8.5 Hz, 1H), 2.74 - 2.62 (m, 2H), 2.40 - 2.29 (m, 2H), 1.97 - 1.81 (m, 2H), 1.70 (dd, *J*=13.1, 7.0 Hz, 1H), 1.64 - 1.49 (m, 8H), 1.49 - 1.34 (m, 6H), 1.32 - 1.12 (m, 6H), 1.06 (s, 3H), 0.93 (d, *J*=12.5 Hz, 3H), 0.98 - 0.88 (m, 3H), 0.77 (t, *J*=11.9 Hz, 1H); MS: MS *m/z* 850.6 (M^++1).

Preparation of Compound 6115 and Compound 6116



Compound 6115



Compound 6116

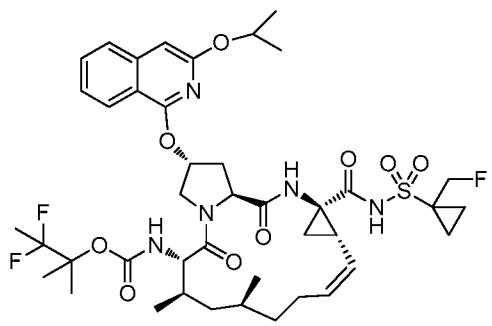
Compounds 6115 and 6116 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6115: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 868.5 (M^++1).

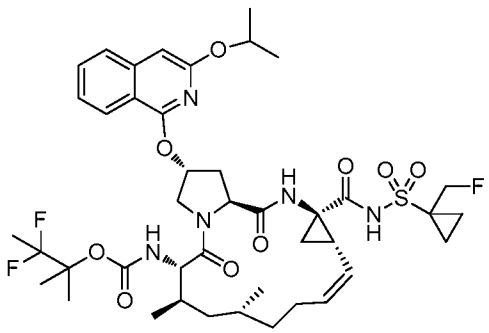
Compound 6116: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ11.28 (s, 1H), 9.05 (s, 1H), 8.00 (d, *J*=8.2 Hz, 1H), 7.85 (d, *J*=7.9 Hz, 1H), 7.71 (d, *J*=8.2 Hz, 1H), 7.62 (d, *J*=7.9 Hz, 1H), 7.29 (t, *J*=7.8 Hz, 1H), 6.67 (s, 1H), 5.80 (br. s., 1H), 5.60 - 5.46 (m, 1H), 5.18 - 5.08 (m, 1H), 5.00 (t, *J*=10.2 Hz, 1H), 4.59 (d, *J*=12.5 Hz, 1H), 4.55 - 4.45 (m, 1H), 4.00 - 3.90 (m, 2H), 3.72 (dd, *J*=10.7, 8.2 Hz, 1H), 2.70 - 2.60 (m, 2H), 2.38 - 2.27 (m, 2H), 1.96 - 1.82 (m, 2H), 1.76 - 1.65 (m, 2H), 1.54 (m, 4H), 1.43 (m, 1H), 1.40 - 1.34 (m, 10H), 1.29 -

1.21 (m, 2H), 1.15 (d, *J*=12.2 Hz, 1H), 1.10 (s, 3H), 0.99 - 0.85 (m, 6H), 0.76 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 868.5 (M^++1).

Preparation of Compound 6117 and Compound 6118



Compound 6117



Compound 6118

Compounds 6117 and 6118 were prepared using the intermediates described herein and by following the general procedure described for the synthesis of Compound 3117:

Compound 6117: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. MS: MS *m/z* 864.6 (M^++1).

Compound 6118: 3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.29 (s, 1H), 9.02 (s, 1H), 8.00 (d, *J*=8.5 Hz, 1H), 7.71 (d, *J*=8.5 Hz, 1H), 7.67 - 7.58 (m, 2H), 7.28 (t, *J*=7.5 Hz, 1H), 6.67 (s, 1H), 5.80 (br. s., 1H), 5.59 - 5.43 (m, 1H), 5.19 - 5.09 (m, 1H), 5.01 (t, *J*=9.9 Hz, 1H), 4.59 (dd, *J*=11.1, 6.3 Hz, 1H), 4.52 - 4.44 (m, 1H), 3.99 - 3.89 (m, 1H), 3.74 (dd, *J*=10.5, 8.4

Hz, 1H), 2.72 - 2.60 (m, 2H), 2.38 - 2.26 (m, 2H), 1.95 - 1.81 (m, 2H), 1.70 (dd, *J*=13.1, 7.3 Hz, 1H), 1.63 - 1.51 (m, 7H), 1.44 (br. s., 1H), 1.37 (m, 8H), 1.32 - 1.19 (m, 6H), 1.16 (m, 1H), 1.04 (s, 3H), 0.98 - 0.88 (m, 6H), 0.76 (t, *J*=12.5 Hz, 1H); MS: MS *m/z* 864.6 (M^++1).

Biological Studies

HCV NS3/4A protease complex enzyme assays and cell-based HCV replicon assays were utilized in the present disclosure, and were prepared, conducted and validated as follows:

Generation of recombinant HCV NS3/4A protease complex

HCV NS3 protease complexes, derived from the BMS strain, H77 strain or J4L6S strain, were generated, as described below. These purified recombinant proteins were generated for use in a homogeneous assay (see below) to provide an indication of how effective compounds of the present disclosure would be in inhibiting HCV NS3 proteolytic activity.

Serum from an HCV-infected patient was obtained from Dr. T. Wright, San Francisco Hospital. An engineered full-length cDNA (compliment deoxyribonucleic acid) template of the HCV genome (BMS strain) was constructed from DNA fragments obtained by reverse transcription-PCR (RT-PCR) of serum RNA (ribonucleic acid) and using primers selected on the basis of homology between other genotype 1a strains. From the determination of the entire genome sequence, a genotype 1a was assigned to the HCV isolate according to the classification of Simmonds et al. (See P Simmonds, KA Rose, S Graham, SW Chan, F McOmish, BC Dow, EA Follett, PL Yap and H Marsden, *J. Clin. Microbiol.*, 31(6), 1493-1503 (1993)). The amino acid sequence of the nonstructural region, NS2-5B, was shown to be >97% identical to HCV genotype 1a (H77) and 87% identical to genotype 1b (J4L6S). The infectious clones, H77 (1a genotype) and J4L6S (1b genotype) were obtained from R. Purcell (NIH) and the sequences are published in Genbank (AAB67036, see Yanagi,M., Purcell,R.H., Emerson,S.U. and Bukh, *J. Proc. Natl. Acad. Sci. U.S.A.* 94(16), 8738-8743 (1997); AF054247, see Yanagi,M., St Claire,M., Shapiro,M., Emerson,S.U., Purcell,R.H. and Bukh, J., *Virology* 244 (1), 161-172. (1998)).

The H77 and J4L6S strains were used for production of recombinant NS3/4A protease complexes. DNA encoding the recombinant HCV NS3/4A protease complex (amino acids 1027 to 1711) for these strains was manipulated as described by P. Gallinari et al. (see Gallinari P, Paolini C, Brennan D, Nardi C, Steinkuhler C, De Francesco R. *Biochemistry*. 38(17):5620-32, (1999)). Briefly, a three-lysine solubilizing tail was added at the 3'-end of the NS4A coding region. The cysteine in the P1 position of the NS4A-NS4B cleavage site (amino acid 1711) was changed to a glycine to avoid the proteolytic cleavage of the lysine tag. Furthermore, a cysteine to serine mutation was introduced by PCR at amino acid position 1454 to prevent the autolytic cleavage in the NS3 helicase domain. The variant DNA fragment was cloned in the pET21b bacterial expression vector (Novagen) and the NS3/4A complex was expressed in Escherichia. coli strain BL21 (DE3) (Invitrogen) following the protocol described by P. Gallinari et al. (see Gallinari P, Brennan D, Nardi C, Brunetti M, Tomei L, Steinkuhler C, De Francesco R., *J Virol*. 72(8):6758-69 (1998)) with modifications. Briefly, the NS3/4A protease complex expression was induced with 0.5 millimolar (mM) Isopropyl β-D-1-thiogalactopyranoside (IPTG) for 22 hours (h) at 20°C. A typical fermentation (1 Liter (L)) yielded approximately 10 grams (g) of wet cell paste. The cells were resuspended in lysis buffer (10 mL/g) consisting of 25 mM *N*-(2-Hydroxyethyl)Piperazine-*N*'-(2-Ethane Sulfonic acid) (HEPES), pH 7.5, 20% glycerol, 500 mM Sodium Chloride (NaCl), 0.5% Triton X-100, 1 microgram/milliliter ("μg/mL") lysozyme, 5 mM Magnesium Chloride ($MgCl_2$), 1 μg/ml DnaseI, 5 mM β-Mercaptoethanol (βME), Protease inhibitor-Ethylenediamine Tetraacetic acid (EDTA) free (Roche), homogenized and incubated for 20 minutes (min) at 4°C. The homogenate was sonicated and clarified by ultra-centrifugation at 235000 g for 1 hour (h) at 4°C. Imidazole was added to the supernatant to a final concentration of 15 mM and the pH adjusted to 8.0. The crude protein extract was loaded on a Nickel-Nitrilotriacetic acid (Ni-NTA) column pre-equilibrated with buffer B (25 mM HEPES, pH 8.0, 20% glycerol, 500 mM NaCl, 0.5% Triton X-100, 15 mM imidazole, 5 mM βME). The sample was loaded at a flow rate of 1 mL/min. The column was washed with 15 column volumes of buffer C (same as buffer B except with 0.2% Triton X-100). The protein was eluted with 5 column volumes of buffer D (same as buffer C except with 200 mM Imidazole).

NS3/4A protease complex-containing fractions were pooled and loaded on a desalting column Superdex-S200 pre-equilibrated with buffer D (25 mM HEPES, pH 7.5, 20% glycerol, 300 mM NaCl, 0.2% Triton X-100, 10 mM βME). Sample was loaded at a flow rate of 1 mL/min. NS3/4A protease complex-containing fractions were pooled and concentrated to approximately 0.5 mg/ml. The purity of the NS3/4A protease complexes, derived from the BMS, H77 and J4L6S strains, were judged to be greater than 90% by SDS-PAGE and mass spectrometry analyses. The enzyme was stored at -80 °C, thawed on ice and diluted prior to use in assay buffer.

FRET peptide assay to monitor HCV NS3/4A proteolytic activty

The purpose of this in vitro assay was to measure the inhibition of HCV NS3 protease complexes, derived from the BMS strain, H77 strain or J4L6S strain, as described above, by compounds of the present disclosure. This assay provides an indication of how effective compounds of the present disclosure would be in inhibiting HCV NS3 proteolytic activity.

In order to monitor HCV NS3/4A protease activity, an NS3/4A peptide substrate was used. The substrate was RET S1 (Resonance Energy Transfer Depsipeptide Substrate; AnaSpec, Inc. cat # 22991)(FRET peptide), described by Taliani et al. in *Anal. Biochem*. 240(2):60-67 (1996). The sequence of this peptide is loosely based on the NS4A/NS4B natural cleavage site for the HCV NS3 protease except there is an ester linkage rather than an amide bond at the cleavage site. The peptide also contains a fluorescence donor, EDANS, near one end of the peptide and an acceptor, DABCYL, near the other end. The fluorescence of the peptide is quenched by intermolecular resonance energy transfer (RET) between the donor and the acceptor, but as the NS3 protease cleaves the peptide the products are released from RET quenching and the fluorescence of the donor becomes apparent.

The peptide substrate was incubated with one of the three recombinant NS3/4A protease complexes, in the absence or presence of a compound of the present disclosure. The inhibitory effects of a compound were determined by monitoring the formation of fluorescent reaction product in real time using a Cytofluor Series 4000.

The reagents were as follow: HEPES and Glycerol (Ultrapure) were obtained

from GIBCO-BRL. Dimethyl Sulfoxide (DMSO) was obtained from Sigma. β-Mercaptoethanol was obtained from Bio Rad.

Assay buffer: 50 mM HEPES, pH 7.5; 0.15 M NaCl; 0.1% Triton; 15% Glycerol; 10 mM βME. Substrate: 2 μM final concentration (from a 2 mM stock solution in DMSO stored at -20°C). HCV NS3/4A protease type 1a (1b), 2-3 nM final concentration (from a 5 μM stock solution in 25 mM HEPES, pH 7.5, 20% glycerol, 300 mM NaCl, 0.2% Triton-X100, 10 mM βME). For compounds with potencies approaching the assay limit, the assay was made more sensitive by adding 50 μg/ml Bovine Serum Albumin (Sigma) to the assay buffer and reducing the end protease concentration to 300 pM.

The assay was performed in a 96-well polystyrene black plate from Falcon. Each well contained 25 μl NS3/4A protease complex in assay buffer, 50 μl of a compound of the present disclosure in 10% DMSO/assay buffer and 25 μl substrate in assay buffer. A control (no compound) was also prepared on the same assay plate. The enzyme complex was mixed with compound or control solution for 1 min before initiating the enzymatic reaction by the addition of substrate. The assay plate was read immediately using the Cytofluor Series 4000 (Perspective Biosystems). The instrument was set to read an emission of 340 nm and excitation of 490 nm at 25°C. Reactions were generally followed for approximately 15 min.

The percent inhibition was calculated with the following equation:

$$100-[(\delta F_{inh}/\delta F_{con})x100]$$

where δF is the change in fluorescence over the linear range of the curve. A non-linear curve fit was applied to the inhibition-concentration data, and the 50% effective concentration (IC_{50}) was calculated by the use of Excel XLfit software using the equation, y=A+((B-A)/(1+((C/x)^D))).

Compounds of the present disclosure, which were tested against more than one type of NS3/4A complex, were found to have similar inhibitory properties though the compounds uniformly demonstrated greater potency against the 1b strains as compared to the 1a strains.

Generation of HCV Replicon

An HCV replicon whole cell system was established as described by

Lohmann V, Korner F, Koch J, Herian U, Theilmann L, Bartenschlager R., Science 285(5424):110-3 (1999) and modified to introduce a luciferase reporter, as first described by Krieger et al (Krieger N, Lohmann V, and Bartenschlager R, *J. Virol.* 75(10):4614-4624 (2001)). CDNA encoding a humanized form of the Renilla luciferase gene and a linker sequence fused directly to the 3'-end of the luciferase gene were introduced into the replicon construct using an Asc1 restriction site located in core, directly upstream of the neomycin marker gene. The adaptive mutation at position 1179 (serine to isoleucine) was also introduced (Blight KJ, Kolykhalov, AA, Rice, CM, *Science* 290(5498):1972-1974). A stable cell line constitutively expressing this HCV replicon construct was generated by first linearizing plasmid DNAs with ScaI. RNA transcripts were synthesized in vitro using the T7 MegaScript transcription kit (Ambion, Austin, TX) according to manufacturer's directions. In vitro transcripts of the cDNA were transfected into the human hepatoma cell line, HUH-7. Selection for cells constitutively expressing the HCV replicon was achieved in the presence of the selectable marker, neomycin (G418). Resulting cell lines were characterized for positive and negative strand RNA production and protein production over time.

A stable HCV replicon luciferase reporter cell line representing the genotype 1a H77 strain (Yanagi M, Purcell RH, Emerson SU, et al. Transcripts from a single full-length cDNA clone of hepatitis C virus are infectious when directly transfected into the liver of a chimpanzee. Proc Natl Acad Sci USA 1997; 94(16):8738-8743) was generated as described previously for the genotype 1b(Con1) replicon luciferase cell line. The replicon construct was modified by introducing mutations were introduced into the genes encoding the NS3 helicase domain (proline replaced by leucine at position 1496) and NS5A (serine to isoleucine at position 2204) to improve replication in cell culture.

HCV Replicon Luciferase Reporter Assay

HCV replicon luciferase assays were developed to monitor the inhibitory effects of compounds described in the disclosure on HCV genotypes 1a and 1b viral replication. HUH-7 cells, constitutively expressing the HCV replicon, were grown in Dulbecco's Modified Eagle Media (DMEM) (Gibco-BRL) containing 10% Fetal calf

serum (FCS) (Sigma) and 1 mg/mL G418 (Gibco-BRL). Compounds were serially diluted 3 folds in DMSO for a twenty-point titration and subsequently transferred to sterile 384-well tissue-culture treated plates (Corning cat # 3571). The plates were then seeded with 50 μL of cells at a density of 3.0 x 10^3 cells/well in DMEM containing 4 % FCS (final DMSO concentration at 0.5 %). After 3 days incubation at 37°C, cells were analyzed for Renilla Luciferase activity using the EnduRen as substrate (Promega cat #E6485). The EnduRen substrate was diluted in DMEM and then added to the plates to a final concentration of 7.5 μM. The plates were incubated for 2 hrs at 37°C and then read immediately for 30 seconds with Viewlux Imager (PerkinElmer) using a luminescence program. To assess cytotoxicity of compounds, CC_{50} values were generated by multiplexing the EnduRen-containing plates with Cell Titer-Blue (Promega, cat # G8082). Cell-Titer Blue (3 μL) was added to each well and incubated for 8 hrs at 37°C. The fluorescence signal from each well was read, with an excitation wavelength at 525/10 nm and an emission wavelength of 598/10 nm, using the Viewlux Imager.

The EC_{50} values for compounds were calculated by using a four-parameter logistic equation:

$$y = A+((B-A)/(1+((C/x)^D))),$$

where A and B denotes minimal and maximal % inhibition, respectively, C is the EC_{50}, D is the hill slope and x represents compound concentration.

Table 2 shows the EC50 values of representative compounds of the present disclosure. Ranges are as follows: A = 0.10 nM - 0.50 nM; B = 0.51 nM - 1.00 nM; C = 1.01 nM - 5.00 nM; D = 5.01 nM - 35.00 nM; E = 35.01 nM-620 nM.

Table 2

Patent Compound Number	LE_1a (EC50, nM)	LE_1b (EC50, nM)	LE_1a (EC50, range)	LE_1b (EC50, range)
3			A	A
5				
6				
7			A	A

9			A	A
10	3.08	0.80	A	A
11			A	A
14			A	A
15			A	A
16			A	A
18			A	A
20			A	A
22	0.43	0.40	A	A
24			A	A
25			B	B
27			A	A
28			A	A
30			A	A
32			A	A
1001	1000.00	449.10	C	C
1002			C	B
1003			C	C
1004	109.70	48.77	C	B
1005			C	C
1006			B	B
1007	1000.00	438.40	C	C
1008			B	B
1009			C	C
1010			B	B
1011	1000.00	362.30	C	C
1012			B	B
1013			C	C
1014			B	B
1015			C	C
1016			B	B
1017			C	C
1018			B	B
1019	1000.00	506.00	C	C
1020			B	B
1021			C	C
1022			B	B
1023				C

1024			B	B
1025			B	A
1026			A	A
1027			A	A
1028			A	A
1029			B	B
1030			A	A
1031			B	B
1032			A	A
1033			A	A
1034			A	A
1035			B	B
1036			A	A
1037			B	B
1038			A	A
1039			A	A
1040			A	A
1041			B	A
1042				
1043			A	A
1044			A	A
1045			A	A
1046			A	A
1047			B	B
1048			A	A
1049			B	B
1050			A	A
1051			B	B
1052			B	A
1053			B	B
1054			A	A
1055			A	A
1056			A	A
1057			A	A
1058			A	A
1059			B	B
1060			A	A
1061			B	B

1062			A	A
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1079			B	A
1080			A	A
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1088			A	A
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1097			B	A
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1099			A	A

1100			A	A
1101			B	B
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1104			A	A
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1106			A	A
1107			B	A
1108			A	A
1109				
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1113			A	A
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1116			A	A
1117			A	A
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1122			A	A
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1124			A	A
1125			A	A
1126			B	A
1127			A	A
1128			A	A
1129			A	A
1130			A	A
1131			A	A
1132			A	A
1133			A	A
1134			C	C
1135			B	A
1136			C	C
1137			B	A

1138			C	C
1139			B	B
1140			A	A
1141			A	A
1142				A
1143			B	A
1144			A	A
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1169			A	A
1170			B	B
1171			A	A
1172			C	B
1173			A	A
1173			B	A
1174			B	B

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1177			A	A
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1182			A	A
2001			B	B
2002			B	B
2003	329.70	157.80	C	C
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3172	1.04	1.18	A	A
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4109			A	A
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4111			C	B
4112			C	C
4113			C	C
4114			B	B
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4163	9.80	1.89	B	A
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4165			A	A
4166			A	A
4167			A	A
4168				
4169			A	A
4170			C	B
4171			A	A
4172			A	A
4173			A	A
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4184				

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4207			A	A
4208			B	A
4209				
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4216				
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4225			A	A
4226				
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4230			A	A
4231			A	A
4232				
4234				
4235			B	B
4236			A	A
4237			A	A
4238			B	B
4239			A	A
5001			A	A
5002			A	A
5003	5.46	1.96	B	A
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5007			A	A
5008			A	A
5009			A	A
5010			A	A
5011	41.15	14.17	B	B
5012			A	A
5013			A	A
5014			A	A
5015			B	A
5016			A	A
5017			B	A
5018			A	A
5019	7.27	3.65	B	A
5020			A	A
5021			B	A
5022			A	A
5023	16.02	24.64	B	B
5024			A	A

5025			B	A
5026			A	A
5027			A	A
5028	6.28	2.96	B	A
5029			A	A
5030			B	B
5031			A	A
5032			B	B
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5036			B	B
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5038			B	B
5039			A	A
5040			C	C
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5043			A	A
5044			B	B
5045			A	A
5046			B	A
5047			A	A
5048			B	B
5049			A	A
5050			B	B
5051			A	A
5052	330.40	76.16	C	B
5053			B	A
5054			C	C
5055			B	A
5056	255.80	61.03	C	B
5057			A	A
5058			C	C
5059			B	B
5060	1000.00	950.10	C	C
5061			B	B
5062	1000.00	1000.00	C	C

5063	1000.00	478.70	C	C
5064			C	B
5065			B	A
5066			C	C
5067			B	B
5068			C	C
5069	14.95	7.21	B	B
5070			B	A
5071	1000.00	1000.00	C	C
5072			C	B
5073			C	C
5074			B	B
5075	1000.00	1000.00	C	C
5076			C	C
5077			B	B
5078	28.89	8.73	B	B
5079			A	A
5080			C	B
5081			B	A
5082	198.00	45.51	C	B
5083			A	A
5084	520.20	131.00	C	C
5085			B	B
5086	411.40	155.00	C	C
5087			A	A
5088	102.80	20.30	C	B
5089			A	A
5090	521.50	87.44	C	B
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5092			C	B
5093			B	A
5094			C	C
5095			B	B
5096			C	B
5097			A	A
5098			C	C
5099			A	A
5100			A	A

5101			A	A
5102			A	A
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5111			A	A
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5114				
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5116			C	B
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5118			B	B
5119			A	A
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5214			B	A

5215			A	A
5216			B	A
5217			A	A
5218			A	A
5219			A	A
5220			A	A
5221			A	A
5222			B	A
5223			A	A
5224			B	B
5225			A	A
5226			B	B
5227			A	A
5228			B	A
5229			A	A
5230			B	A
5231			A	A
5232				
5233			A	A
5234				
5235			A	A
5236			A	A
5237			A	A
5238				
5239			A	A
5240				
5241			A	A
5242				
5243			A	A
5244			B	B
5245			A	A
5246			B	B
5247			A	A
5248			B	A
5249			A	A
5250	22.64	5.50	B	B
5251			A	A
5251				

5252	15.08	4.04	B	A
5253			A	A
5254			B	A
5255			A	A
5256	20.87	12.95	B	B
5257			A	A
5258			B	A
5259			A	A
5260			A	A
5261	14.26	2.18	B	A
5262			A	A
5263			B	A
5264			A	A
5265			B	A
5266			A	A
5267			B	B
5268			A	A
5269			B	B
5270			A	A
5271			B	B
5272			A	A
5273			B	B
5274			A	A
5275			A	A
5276			A	A
5277			A	A
5278			A	A
5279			B	B
5280			A	A
5281			A	A
5282			A	A
5283	4.82	3.12	A	A
5284			A	A
5285			B	A
5286			A	A
5287			A	A
5288			A	A
5289			B	A

5290	1.25	0.64	A	A
5291			A	A
5292			A	A
5293			B	A
5294			A	A
5295			B	A
5296			A	A
5297	7.06	3.16	B	A
5298			A	A
5299			A	A
5300			A	A
5301			B	A
5302			A	A
5303			B	A
5304			A	A
5305			B	B
5306	2.97	2.45	A	A
5307			B	A
5308			A	A
5309			B	A
5310			A	A
5311			A	A
5312			A	A
5313			A	A
5314	1.59	1.06	A	A
5315			B	B
5316			A	A
5317			B	B
5318			A	A
5319	33.59	14.25	B	B
5320			A	A
5321			A	A
5322			A	A
5323			A	A
5324			A	A
5325				
5326			A	A
5327				

5328			A	A
5329				
5330			A	A
5331	12.82	3.94	B	A
5332			A	A
5333			B	B
5334			A	A
5335	6.50	2.03	B	A
5336			A	A
5337			B	A
5338			A	A
5339			B	A
5340			A	A
5341			A	A
5342			A	A
5343				
5344			A	A
5345			B	A
5346			A	A
5347				
5348			A	A
5349			B	A
5350	2.12	1.48	A	A
5352			A	A
5353			B	A
5354			A	A
6001			A	A
6002			B	A
6003	1.33	0.22	A	A
6004			B	A
6005	1.29	0.28	A	A
6006				
6007			A	A
6008			A	A
6009	1.12	0.30	A	A
6010				
6011			A	A
6012				

6013			A	A
6014				
6015	1.19	0.24	A	A
6016			A	A
6017			A	A
6018			A	A
6019				
6020			A	A
6021				
6022			A	A
6023			B	B
6024			A	A
6025				
6026	1.13	0.70	A	A
6027				
6028			A	A
6029			B	B
6030	1.43	0.81	A	A
6031			B	B
6032			A	A
6033	10.71	4.38	B	A
6034			A	A
6035				
6036	0.53	0.38	A	A
6037				
6038			A	A

Compound Number	**LE_1a (EC50, nM)**	**LE_1b (EC50, nM)**	**LE_1a (EC50, range)**	**LE_1b (EC50, range)**
1183			C	C
1184			C	C
1185	2.91	0.83	C	B
1186			D	C
1187			D	C
1188			C	B
1189			C	B

1190	1.66	1.12	C	C
1191			D	D
1192			C	B
1193			C	B
1194			D	C
1195			C	C
1196			B	B
1197			C	B
1198	0.50	0.90	A	B
1199			C	C
1200			C	C
1201			C	C
1202			C	B
1203			C	A
1204			C	B
1205	0.62	0.75	B	B
1206			C	C
1207			C	B
1208			D	C
1209	5.66	2.00	D	C
1210			C	B
1211			C	B
1212			C	A
1213			C	B
1214			C	A
4240	1.23	1.09	C	C
4241			C	C
4242			B	B
4243			C	B
4244			C	C

4245			B	A
4246			C	B
4247			C	C
4249			C	B
4250			C	C
4251			C	C
4252			C	B
4253			C	B
4254			C	B
4256			B	A
4257			D	B
4259			C	B
4260			C	C
4261			D	C
4262			E	E
4263			C	B
4265	616.20	475.20	E	E
4266			C	C
4267			D	C
4268			C	C
4269			C	C
4270			C	A
4271			C	A
4272			D	C
4273			D	C
4276			E	E
4277	1000.00	218.10	E	E
4278			E	E
4279			E	E
4283			D	C

4284	0.73	0.42	B	A
4286			C	B
4287			C	C
4289			D	C
4290			C	B
4292			D	D
4294			B	B
4295			B	C
4296	11.86	5.46	D	D
4297			C	C
4298			C	C
4299			B	B
4300			B	B
4301			B	B
4302			C	C
4304			E	D
4305			E	D
4310			B	C
4311			C	C
4312	20.95	12.18	D	D
4313			B	A
4314			C	C
4315			D	C
4316			C	C
4317			C	C
4318			D	C
4319			D	E
4320	15.04	21.86	D	D
4321			D	D
4322			D	D

4323			C	B
4324			C	B
4325			E	D
4326			E	E
4327			D	D
4328			C	C
4331			C	B
4332			C	C
4333			D	D
4334			C	C
4335			D	D
4336			B	B
4337			B	B
4338			C	C
4339			A	A
4340			D	D
4341			C	C
4342			D	E
4343			D	D
4344			C	C
4345			D	E
4346			B	A
4347			D	C
4348			B	A
4349			D	C
4350	1.49	0.88	C	B
4351			D	C
4352			E	E
4353			D	C
4354			E	E

4355			D	D
4356			B	A
4357			C	B
4358			C	C
4360			C	A
4361			E	D
4362			C	B
4363			C	A
4365			D	D
4366	0.58	0.25	B	A
4373			A	A
4374			C	A
4375			C	B
4376			C	A
4377			B	A
4378			C	B
4379			C	B
4380			C	C
4381			C	B
4382			C	B
4383			C	B
3193			C	B
3194	0.62	0.44	B	A
3195			C	B
3196			B	A
3198			B	C
3200			B	B
3202			C	C
3204			B	C
3206			C	C

3208			C	B
3210			C	A
3212			B	A
3214			C	A
3216			C	A
3218			C	A
3220			C	A
3222			C	C
3224			C	C
3226			C	B
5355			C	C
5357			C	B
5359			C	C
5361			B	B
5363			C	B
5365			C	B
5367			B	A
5369			C	C
5371			C	B
5373			C	B
5375			C	B
5377			C	C
5379			C	C
5381			C	C
5383			D	C
5385			D	C
5387			C	C
5389			C	C
5391			C	C
5393	0.92	0.55	B	B

5395			C	B
5397			C	B
5399			B	A
5401			C	A
5403			B	A
5405			C	B
5407			C	B
5409			C	B
5410			D	C
5411			C	B
5413			C	B
5415			C	B
5417			C	C
5419			C	B
5421			C	B
5423			C	B
5425			C	C
5427			D	D
5429			C	C
5431			C	C
5433			B	A
5434			C	C
5435			C	C
5437			C	A
5439			B	A
5441			C	C
5443			C	B
5445			C	C
5447			C	C
5449			C	B

5451			C	C
5453			C	B
5455			C	A
5457			C	B
5459			C	C
5461			C	C
5463			D	D
5465			C	C
5467			C	A
5469			C	A
5471			C	A
5472			C	C
5473			C	A
5474			C	C
5475			B	B
5476			D	C
5477			C	C
5479			C	B
5481			C	C
5483			C	C
5485			C	C
5487			C	C
5489			C	C
5503			C	B
5505			D	C
5507			C	B
5509			C	B
5511			C	C
5513			C	B
5515			C	B

5517			C	C
5519			C	B
5521			C	A
5523			C	B
5525			C	B
5527			C	B
5529			C	A
5531			C	B
5533			C	A
5535			D	C
5537			B	A
5539			C	C
5541			C	B
5543			C	C
5545			B	B
5547			B	C
5549			B	B
5550			B	C
5553	1.13	1.38	C	C
6039			D	D
6040			C	B
6042			C	B
6044			C	A
6046			C	B
6048			C	A
6050			C	A
6052			D	A
6054			C	A
6056			C	A
6058			C	B

6060			C	C
6062			C	B
6064			B	A
6066			C	C
6068			C	B
6070			C	B
6072			C	B
6074			B	C
6076			C	C
6078			C	C
6080	0.31	0.79	A	B
6082			B	C
6084			A	B
6086			D	D
6088			D	D
6090			B	B
6092			C	C
6095			B	A
6098			B	A
6099			C	C
6100			C	A
6102			B	A
6104			C	B
6105			D	C
6106			C	A
6108			B	A
6110			C	B
6112			C	B
6114			C	A
6116			C	C

6118			C	C

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.

CLAIMS

What is claimed is:

1. A compound selected from:

(S)-3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

(R)-3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-(4-isopropoxyphenyl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-3,6-dimethoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-3,6-dimethoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3-(trifluoromethyl)tetrahydro-2H-pyran-3-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-3,6-dimethoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

2-(trifluoromethyl)tetrahydro-2H-pyran-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

2-(trifluoromethyl)tetrahydro-2H-pyran-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

2-(trifluoromethyl)tetrahydro-2H-pyran-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,6-dimethoxyisoquinolin-1-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((8-fluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((8-fluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((8-fluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((8-fluoro-9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-2,7-dimethoxyquinolin-4-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-2,7-dimethoxyquinolin-4-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((6-fluoro-2,7-dimethoxyquinolin-4-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((6-fluoro-2,7-dimethoxyquinolin-4-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-fluoro-2,7-dimethoxyquinolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-fluoro-2,7-dimethoxyquinolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-chloro-4-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-chloro-4-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7,9-dimethyl-

5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,7-dimethoxyquinolin-4-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,7-dimethoxyquinolin-4-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,7-dimethoxyquinolin-4-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2,7-dimethoxyquinolin-4-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,7-dimethoxyquinolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,7-dimethoxyquinolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropoxy-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-(dimethylamino)-4-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-3-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-chloro-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-chloro-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-chloro-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-chloro-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-chloro-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-chloro-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-fluoro-6-methoxy-4-morpholinoisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-(dimethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2-(4-isopropoxyphenyl)-7-methoxyquinolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-fluoro-6-methoxy-4-morpholinoisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-methoxy-2-(1H-pyrazol-1-yl)quinolin-4-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-methoxy-2-(1H-pyrazol-1-yl)quinolin-4-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2-(3-fluoro-4-isopropoxyphenyl)-7-methoxyquinolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((4-ethoxy-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((5-chloro-4-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-methoxy-4-(4-(methylsulfonyl)piperazin-1-yl)isoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-(diethylamino)-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1-(((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-6-((((1,1,1-trifluoro-2-methylpropan-2-yl)oxy)carbonyl)amino)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-2-yl)oxy)-6-methoxyisoquinoline-4-carboxylic acid;

1-(((2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-((tert-butoxycarbonyl)amino)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-2-yl)oxy)-6-methoxyisoquinoline-4-carboxylic acid;

1-(((2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-((tert-butoxycarbonyl)amino)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-2-yl)oxy)-6-methoxyisoquinoline-4-carboxylic acid;

1-(((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-5,16-dioxo-6-((((1,1,1-trifluoro-2-methylpropan-2-yl)oxy)carbonyl)amino)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-2-yl)oxy)-6-methoxyisoquinoline-4-carboxylic acid;

N-((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)thiomorpholine-4-carboxamide 1,1-dioxide;

N-((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)morpholine-4-carboxamide;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-methoxycinnolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-methoxycinnolin-4-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-methoxycinnolin-4-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-methoxycinnolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

(2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-6-(1-(trifluoromethyl)cyclopropanecarboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-6-(3,3,3-trifluoro-2,2-dimethylpropanamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-methoxycinnolin-4-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

N-((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-2,6-dimethylmorpholine-4-carboxamide;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-methoxycinnolin-4-yl)oxy)-9-

methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

(2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-6-(4-methylpiperazine-1-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-6-(1-methyl-1H-pyrazole-3-carboxamido)-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(R)-1,1,1-trifluoropropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((1-chloro-6-methoxyisoquinolin-4-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-fluoro-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

(2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-6-(1-(trifluoromethyl)cyclopropanecarboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-6-(3,3,3-trifluoro-2,2-dimethylpropanamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

N-((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)morpholine-4-carboxamide;

N-((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-2,6-dimethylmorpholine-4-carboxamide;

(2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-6-(4-methylpiperazine-1-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-carbamoyl-6-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-carbamoyl-6-methoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

(2R,6S,7R,9R,13aS,14aR,16aS,Z)-6-(4,4-difluoropiperidine-1-carboxamido)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-carbamoyl-6-methoxyisoquinolin-1-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((4-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((1-chloro-6-methoxyisoquinolin-4-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((1-chloro-6-methoxyisoquinolin-4-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((4-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-

(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(hydroxymethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-14a-(((1-(hydroxymethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-

methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-

dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-

dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6,7-dimethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-

methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-((4-morpholinoisoquinolin-1-yl)oxy)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-2-((4-methyl-3,4-dihydro-2H-[1,4]oxazino[2,3-f]isoquinolin-7-yl)oxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-fluoro-4-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-

methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((3-(5-isopropoxypyridin-2-yl)-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxy-7-fluoroisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((4-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-ethoxyisoquinolin-1-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-[1,4]dioxino[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((4-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((2-(3-fluoro-4-isopropoxyphenyl)-7-methoxyquinolin-4-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2-(4-isopropoxyphenyl)-7-methoxyquinolin-4-yl)oxy)-7-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((2-(4-isopropoxyphenyl)-7-methoxyquinolin-4-yl)oxy)-7-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-fluoro-6-methoxyisoquinolin-1-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[3,2-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-

dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,4-dihydro-2H-pyrano[2,3-f]isoquinolin-7-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1-difluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-7-ethyl-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((9-methoxy-2,3-dihydro-1H-pyrano[2,3-c]isoquinolin-6-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-

dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-ethoxyisoquinolin-1-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-isopropoxyisoquinolin-1-

yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; and

3,3-difluoro-2-methylbutan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-2-((3-isopropoxyisoquinolin-1-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; or a pharmaceutically acceptable salt thereof.

2. A compound selected from:

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-chloro-7-methoxyquinoxalin-2-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-chloro-7-methoxyquinoxalin-2-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(4-isopropoxyphenyl)-6-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-(4-isopropoxyphenyl)-6-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-hydroxy-7-methoxyquinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((6-fluoro-3-hydroxy-7-methoxyquinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-chloro-7-methoxyquinoxalin-2-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-chloro-7-methoxyquinoxalin-2-yl)oxy)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-isopropyl-7-methoxyquinoxalin-2-

yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-fluoro-7-methoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,4-dichloro-6-ethoxyquinolin-3-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(dimethylamino)-6-methoxyquinoxalin-2-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-(dimethylamino)-6-methoxyquinoxalin-2-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3-isopropyl-7-methoxyquinoxalin-2-yl)oxy)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-isopropoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-isopropoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-7-ethyl-2-((7-isopropoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-isopropoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-ethoxy-3-hydroxyquinoxalin-2-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((7-isopropoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((7-methoxy-3-methylquinoxalin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((7-ethoxy-3-(trifluoromethyl)quinoxalin-2-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; and

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-7-ethyl-2-((6-fluoro-7-methoxy-3-methylquinoxalin-2-yl)oxy)-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

or a pharmaceutically acceptable salt thereof.

3. A compound selected from:

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyquinolin-3-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyquinolin-3-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,4-dichloro-6-ethoxyquinolin-3-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyquinolin-3-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((6-ethoxyquinolin-3-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,6-dimethoxyquinolin-3-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,6-dimethoxyquinolin-3-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; and

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((2,6-dimethoxyquinolin-3-yl)oxy)-14a-(((1-(fluoromethyl)cyclopropyl)sulfonyl)carbamoyl)-7,9-dimethyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; or a pharmaceutically acceptable salt thereof.

4. A compound selected from:

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-chloro-7-methoxyquinolin-2-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-chloro-7-methoxyquinolin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; and

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((4-chloro-7-methoxyquinolin-2-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;
or a pharmaceutically acceptable salt thereof.

5. A compound selected from:

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-methoxyquinoxalin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3-methoxyquinoxalin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,7-dimethoxy-2-(trifluoromethyl)quinoxalin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

tert-butyl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,7-dimethoxy-2-(trifluoromethyl)quinoxalin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,7-dimethoxy-2-(trifluoromethyl)quinoxalin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9S,13aS,14aR,16aS,Z)-2-((3,7-dimethoxy-2-(trifluoromethyl)quinoxalin-6-yl)oxy)-7,9-dimethyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-14a-((cyclopropylsulfonyl)carbamoyl)-2-((3,7-dimethoxy-2-(trifluoromethyl)quinoxalin-6-yl)oxy)-7-ethyl-9-methyl-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

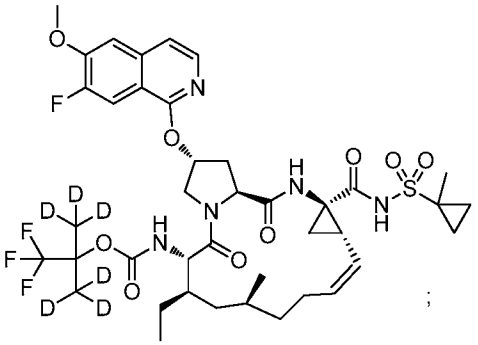
tert-butyl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,7-dimethoxy-2-(trifluoromethyl)quinoxalin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate; and

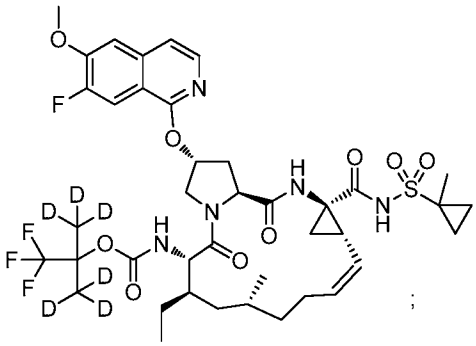
1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,7R,9R,13aS,14aR,16aS,Z)-2-((3,7-dimethoxy-2-(trifluoromethyl)quinoxalin-6-yl)oxy)-7-ethyl-9-methyl-14a-(((1-

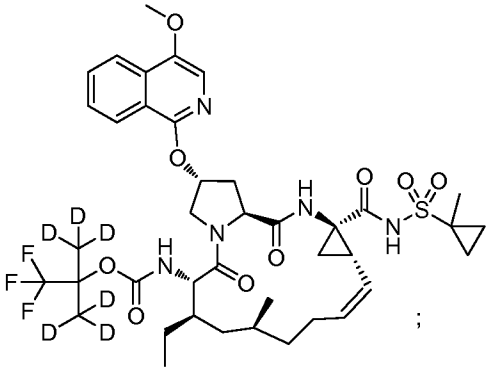
methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)carbamate;

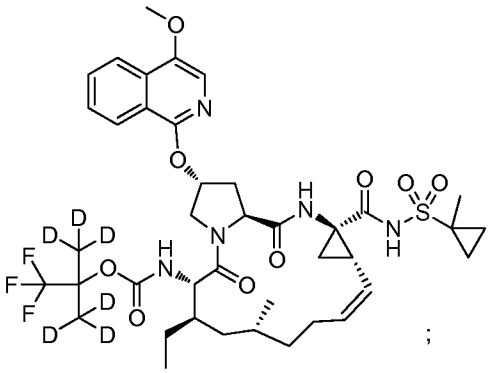
or a pharmaceutically acceptable salt thereof.

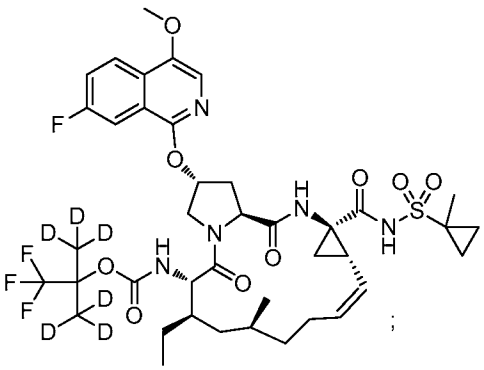
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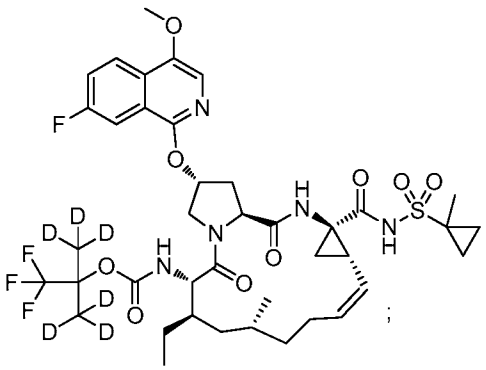

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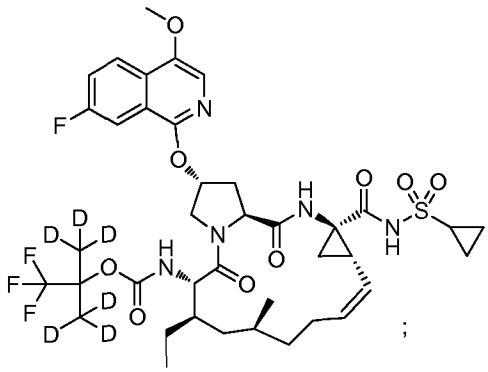

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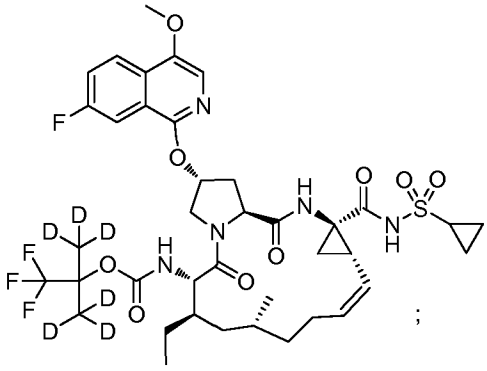

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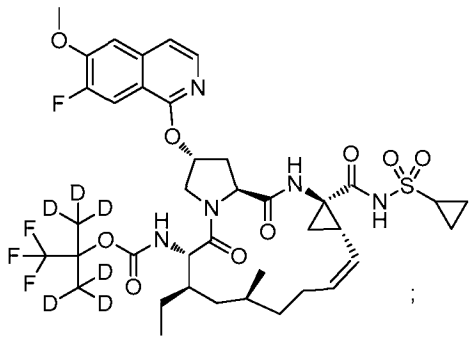

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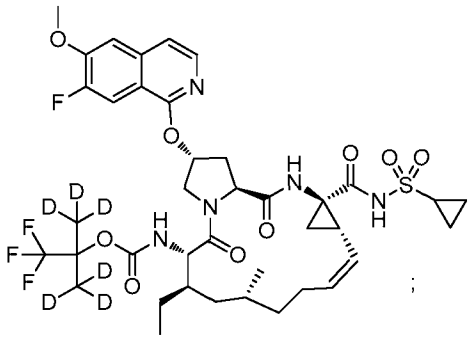

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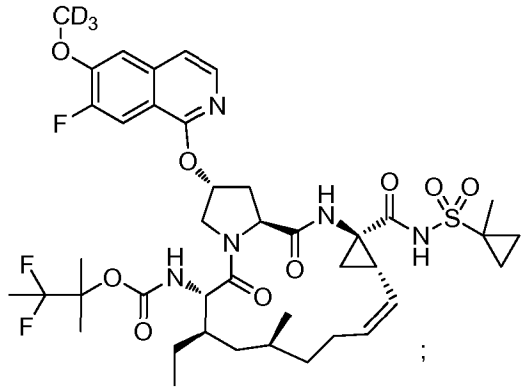

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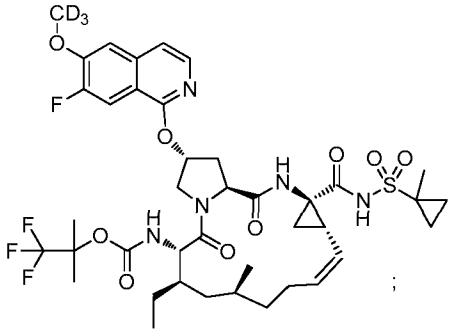

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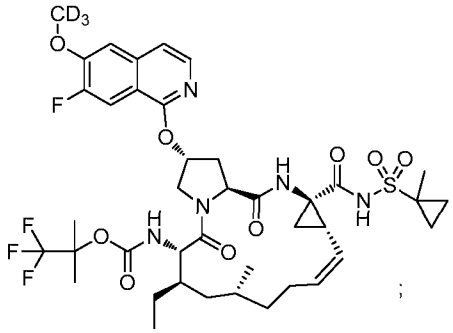

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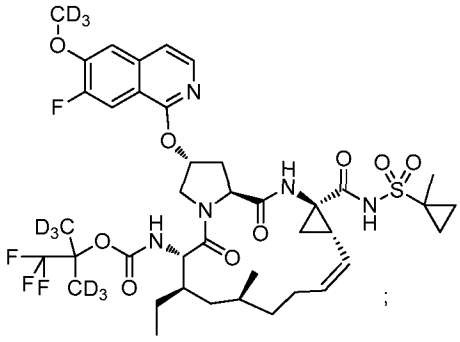
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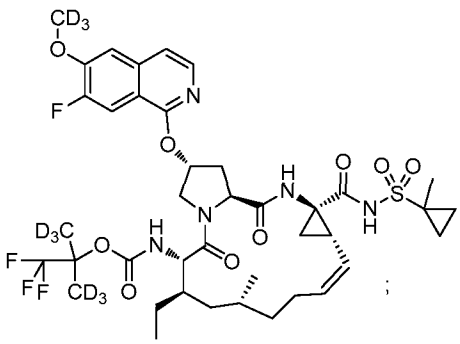
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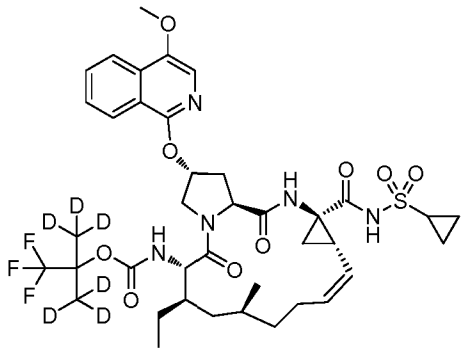
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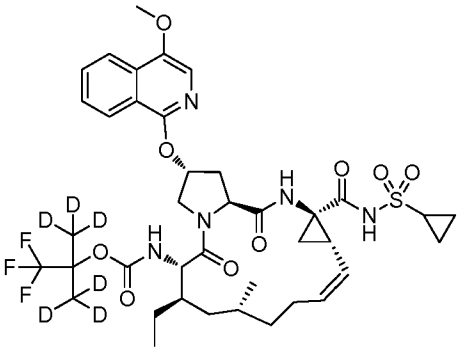


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; and

or a pharmaceutically acceptable salt thereof.

7. A composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

8. A composition comprising a compound of claim 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

9. A composition comprising a compound of claim 3, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10. A composition comprising a compound of claim 4, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

11. A composition comprising a compound of claim 5, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

12. A composition comprising a compound of claim 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

13. The use of a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of HCV infection.

14. The use of a therapeutically effective amount of a compound of claim 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of HCV infection.

15. The use of a therapeutically effective amount of a compound of claim 3, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of HCV infection.

16. The use of a therapeutically effective amount of a compound of claim 4, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of HCV infection.

17. The use of a therapeutically effective amount of a compound of claim 5, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of HCV infection.

18. The use of a therapeutically effective amount of a compound of claim 6, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of HCV infection.