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Fortsættes ...

(54) Benævnelse: **HÆMMERE AF HEPATITIS C-VIRUS**

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DESCRIPTION

FIELD

[0001] Novel small molecule inhibitors of viral replication are disclosed, compositions containing such compounds, and therapeutic methods comprising the administration of such compounds are also disclosed.

BACKGROUND

[0002] The hepatitis C virus (HCV), a member of the hepacivirus genera within the *Flaviviridae* family, is the leading cause of chronic liver disease worldwide (Boyer, N. et al. J Hepatol. 2000, 32, 98-112). Consequently, a significant focus of current antiviral research is directed toward the development of improved methods for the treatment of chronic HCV infections in humans (Ciesek, S., von Hahn T., and Manns, MP., Clin. Liver Dis., 2011, 15, 597-609 ; Soriano, V. et al, J. Antimicrob. Chemother., 2011, 66, 1573-1686; Brody, H., Nature Outlook, 2011, 474, S1-S7; Gordon, C. P., et al J. Med. Chem. 2005, 48, 1-20; Maradpour, D., et al., Nat. Rev. Micro. 2007, 5, 453-463).

[0003] Virologic cures of patients with chronic HCV infection are difficult to achieve because of the prodigious amount of daily virus production in chronically infected patients and the high spontaneous mutability of HCV (Neumann, et al., Science 1998, 282, 103-7; Fukimoto, et al., Hepatology, 1996, 24, 1351-4; Domingo, et al., Gene 1985, 40, 1-8; Martell, et al., J. Virol. 1992, 66, 3225-9). HCV treatment is further complicated by the fact that HCV is genetically diverse and expressed as several different genotypes and numerous subtypes. For example, HCV is currently classified into six major genotypes (designated 1-6), many subtypes (designated a, b, c, and so on), and about 100 different strains (numbered 1, 2, 3, and so on).

[0004] HCV is distributed worldwide with genotypes 1, 2, and 3 predominate within the United States, Europe, Australia, and East Asia (Japan, Taiwan, Thailand, and China). Genotype 4 is largely found in the Middle East, Egypt and central Africa while genotype 5 and 6 are found predominantly in South Africa and South East Asia respectively (Simmonds, P. et al. J Virol. 84: 4597-4610, 2010).

[0005] The combination of ribavirin, a nucleoside analog, and interferon-alpha (α) (IFN), is utilized for the treatment of multiple genotypes of chronic HCV infections in humans. However, the variable clinical response observed within patients and the toxicity of this regimen have limited its usefulness. Addition of a HCV protease inhibitor (telaprevir or boceprevir) to the ribavirin and IFN regimen improves 12-week post-treatment virological response (SVR12) rates substantially. However, the regimen is currently only approved for genotype 1 patients and toxicity and other side effects remain.

[0006] The use of directing acting antivirals to treat multiple genotypes of HCV infection has proven challenging due to the variable activity of antivirals against the different genotypes. HCV protease inhibitors frequently have compromised *in vitro* activity against HCV genotypes 2 and 3 compared to genotype 1 (See, e.g., Table 1 of Summa, V. et al., Antimicrobial Agents and Chemotherapy, 2012, 56, 4161-4167; Gottwein, J. et al, Gastroenterology, 2011, 141, 1067-1079). Correspondingly, clinical efficacy has also proven highly variable across HCV genotypes. For example, therapies that are highly effective against HCV genotype 1 and 2 may have limited or no clinical efficacy against genotype 3. (Moreno, C. et al., Poster 895, 61st AASLD Meeting, Boston, MA, USA, Oct. 29 - Nov. 2, 2010; Graham, F., et al, Gastroenterology, 2011, 141, 881-889 ; Foster, G.R. et al., EASL 45th Annual Meeting, April 14-18, 2010, Vienna, Austria.) In some cases, antiviral agents have good clinical efficacy against genotype 1, but lower and more variable against genotypes 2 and 3. (Reiser, M. et al., Hepatology, 2005, 41,832-835.) To overcome the reduced efficacy in genotype 3 patients, substantially higher doses of antiviral agents may be required to achieve substantial viral load reductions (Fraser, IP et al., Abstract #48, HEP DART 2011, Koloa, HI, December 2011.)

[0007] Antiviral agents that are less susceptible to viral resistance are also needed. For example, resistance mutations at positions 155 and 168 in the HCV protease frequently cause a substantial decrease in antiviral efficacy of HCV protease inhibitors (Mani, N. Ann Forum Collab HIV Res., 2012, 14, 1-8; Romano, KP et al, PNAS, 2010, 107, 20986-20991; Lenz O, Antimicrobial agents and chemotherapy, 2010, 54,1878-1887.)

[0008] WO2007/016441 discloses macrocyclic peptides that are useful as inhibitors of the hepatitis C virus (HCV) NS3 protease, their synthesis, and their use for treating or preventing HCV infections.

[0009] WO2010/011566 discloses macrocyclic quinoxaline compounds and their use as inhibitors of the hepatitis C virus (HCV)

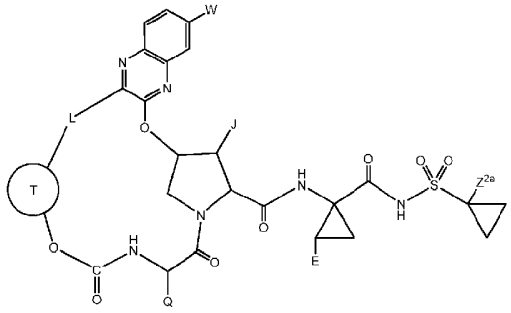
NS3 protease, and in treating or preventing HCV infections.

[0010] In view of the limitations of current HCV therapy, there is a need to develop more effective anti-HCV therapies. It would also be useful to provide therapies that are effective against multiple HCV genotypes and subtypes.

SUMMARY

[0011] Novel compounds that inhibit the hepatitis C virus (HCV) NS3 protease are disclosed. In certain embodiments, the compounds disclosed inhibit multiple genotypes of the hepatitis C virus. These compounds are useful for the treatment of HCV infection and the related symptoms.

[0012] Disclosed is a compound of Formula (IV):



(IV),

or a stereoisomer, or a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, wherein:

J is C_1-C_4 alkyl or C_3-C_6 carbocyclyl, wherein C_1-C_4 alkyl or C_3-C_6 carbocyclyl is optionally substituted with halogen, -OH, aryl or cyano;

Ⓣ

is C_3-C_5 carbocyclylene that is attached to L and to the remainder of the compound through two adjacent carbons, wherein said C_3-C_6 carbocyclylene is optionally substituted with C_1-C_4 alkyl, C_1-C_3 haloalkyl, halogen, -OH, or cyano, or

Ⓣ

is C_5-C_8 bicyclic carbocyclylene that is attached to L and to the remainder of the compound through two adjacent carbons;

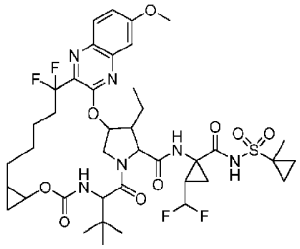
L is C_3-C_6 alkylene, C_3-C_6 alkenylene or-$(CH_2)_3$-cyclopropyl-, optionally substituted with 1-4 halogen, -OH, or cyano;

Q is C_2-C_4 alkyl or C_3-C_6 carbocyclyl optionally substituted with C_1-C_3 alkyl, halogen, -OH, or cyano;

E is C_1-C_3 alkyl or C_2-C_3 alkenyl, optionally substituted with C_1-C_3 alkyl, halogen, -OH, or cyano;

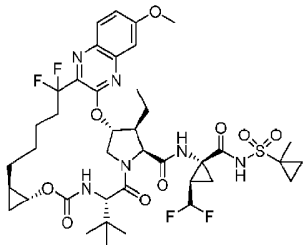
W is H, -OH,-O(C_1-C_3)alkyl, -O(C_1-C_3)haloalkyl, halogen or cyano; and Z^{2a} is H or C_1-C_3 alkyl, halogen, -OH, or cyano.

[0013] In one embodiment, a compound of Formula IVa, or a pharmaceutically acceptable salt thereof, is provided:



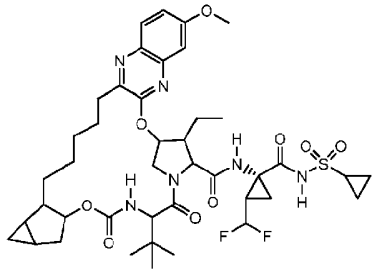
(IVa)

[0014] In one embodiment, a compound of Formula IVb: or a pharmaceutically acceptable salt thereof, is provided:



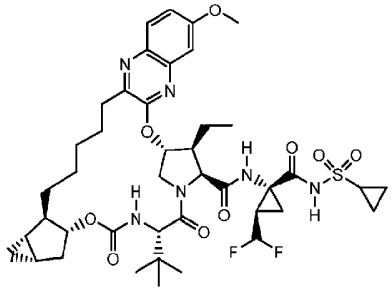
(IVb).

[0015] In one embodiment, a compound of Formula IVc, or a pharmaceutically acceptable salt thereof, is provided:



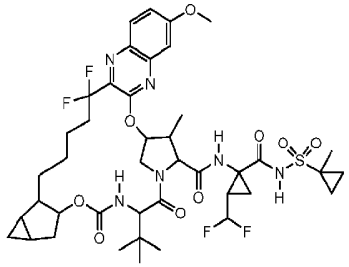
(IVc).

[0016] In one embodiment, a compound of Formula IVd, or a pharmaceutically acceptable salt thereof, is provided:



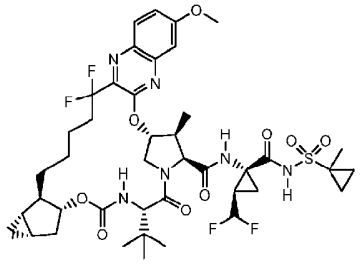
(IVd).

[0017] In one embodiment, a compound of Formula IVe, or a pharmaceutically acceptable salt thereof, is provided:



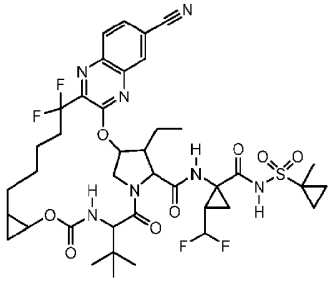
(IVe).

[0018] In one embodiment, a compound of Formula IVf, or a pharmaceutically acceptable salt thereof, is provided:



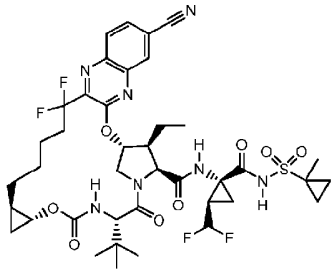
(IVf).

[0019] In one embodiment, a compound of Formula IVg, or a pharmaceutically acceptable salt thereof, is provided:



(IVg).

[0020] In one embodiment, a compound of Formula IVh, or a pharmaceutically acceptable salt thereof, is provided:



(IVh).

[0021] In one embodiment, a compound of any one of Formula IVa, IVb, IVc, IVd, IVe, IVf, IVg, or IVh, or a stereoisomer, or a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, is provided.

Methods of Treatment

[0022] One embodiment provides a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof for use in medical therapy (e.g., for use in treating a *Flaviviridae* viral infection (e.g., an HCV viral infection) or the proliferation of the HCV virus or delaying the onset of HCV symptoms in a patient (e.g., a mammal such as a human).

[0023] One embodiment provides a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for treating a *Flaviviridae* viral infection (e.g., an HCV viral infection) or the proliferation of the HCV virus or delaying the onset of HCV symptoms in a patient in need thereof (e.g., mammal such as a human).

[0024] One embodiment provides a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of the proliferation of a *Flaviviridae* virus, an HCV virus or for use in the therapeutic treatment of delaying the onset of HCV symptoms.

[0025] One embodiment provides a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of a *Flaviviridae* virus infection (e.g., an HCV virus infection).

[0026] One embodiment provides the use of a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for a *Flaviviridae* virus infection (e.g., an HCV virus infection) in a mammal (e.g., a human).

[0027] In certain embodiments, a compound for use in a method of treating chronic hepatitis C infection is provided. The method includes administering to a patient in need thereof, a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof, to the patient.

[0028] In certain embodiments, a compound for use in a method of treating hepatitis C infection in treatment-naïve patients is provided. The method includes administering to a treatment-naïve patient, a compound of Formula IVa-IVh, or a stereoisomer, or a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

[0029] In certain embodiments, a compound for use in a method of treating hepatitis C infection in treatment-experienced patients is provided. The method includes administering to a treatment-experienced patient, a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof.

[0030] In certain embodiments, a compound for use in a of treating hepatitis C infection in an interferon ineligible or an interferon intolerant patient is provided. The method includes administering, a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof, to the patient.

[0031] In certain embodiments, the compound for use in a of treatment described herein include administering the compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof, to the patient for a fixed period of duration. In some embodiments, the fixed period of duration is 4 weeks, 6 weeks, 8 weeks, 10 weeks or 12 weeks. In other embodiments, the fixed period of duration is not more than 12 weeks.

[0032] In some embodiments, the compound is administered for about 12 weeks. In further embodiments, the compound is administered for about 12 weeks or less, for about 10 weeks or less, for about 8 weeks or less, for about 6 weeks or less, or for about 4 weeks or less.

[0033] The compound may be administered once daily, twice daily, once every other day, two times a week, three times a week, four times a week, or five times a week.

[0034] In certain embodiments, the methods of treatment described herein includes administering a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof, to is infected with HCV genotype (GT) 1, 2, 3, 4, 5, or 6 (i.e., a method for treating a GT 1, 2, 3, 4, 5, or 6 HCV infection).

[0035] One embodiment provides a method for treating an HCV infection in a patient in need thereof (e.g., a mammal such as a human), wherein the patient is infected with HCV genotype 1. The method includes administering a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof, to the patient.

[0036] One embodiment provides a compound for use in a method for treating an HCV infection in a patient in need thereof (e.g., a mammal such as a human), wherein the patient is infected with HCV genotype 2. The method includes administering a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof, to the patient.

[0037] One embodiment provides a compound for use in a for treating an HCV infection in a patient in need thereof (e.g., a mammal such as a human), wherein the patient is infected with HCV genotype 3. The method includes administering a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof, to the patient.

[0038] One embodiment provides a compound for use in a method for treating an HCV infection in a patient in need thereof (e.g., a mammal such as a human), wherein the patient is infected with HCV genotype 4. The method includes administering a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof, to the patient.

[0039] One embodiment provides a compound for use in a method for treating an HCV infection in a patient in need thereof (e.g., a mammal such as a human), wherein the patient is infected with HCV genotype 5. The method includes administering a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof, to the patient.

[0040] One embodiment provides a compound for use in a method for treating an HCV infection in a patient in need thereof (e.g., a mammal such as a human), wherein the patient is infected with HCV genotype 6. The method includes administering a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof, to the patient.

[0041] In the methods of treatment described herein, the administering step includes administering a therapeutically effective amount of a compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof, to the patient in need of treatment.

[0042] In certain embodiments, methods of inhibiting the activity of HCV are provided. Such methods include the step of treating a sample suspected of containing HCV with a compound or composition disclosed herein.

[0043] In one embodiment, compounds disclosed herein act as inhibitors of HCV, as intermediates for such inhibitors or have other utilities as described below.

[0044] In certain embodiments, compounds binding in the liver may bind with varying degrees of reversibility.

[0045] In one embodiment, a method for treating HCV includes adding a compound disclosed herein to the sample. The addition step comprises any method of administration as described above.

[0046] If desired, the activity of HCV after application of the compound can be observed by any method including direct and indirect methods of detecting HCV activity. Quantitative, qualitative, and semiquantitative methods of determining HCV activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

[0047] Many organisms contain HCV. The compounds of this invention are useful in the treatment or prophylaxis of conditions associated with HCV activation in animals or in humans.

Pharmaceutical Formulations

[0048] "Pharmaceutically-acceptable" means suitable for use in pharmaceutical preparations, generally considered as safe for such use, officially approved by a regulatory agency of a national or state government for such use, or being listed in the U. S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans.

[0049] "Pharmaceutically-acceptable carrier" refers to a diluent, adjuvant, excipient, or carrier, or other ingredient which is pharmaceutically-acceptable and with which a compound of the invention is administered.

[0050] The compounds of this invention are formulated with conventional carriers (*e.g.*, inactive ingredient or excipient material), which will be selected in accordance with ordinary practice. Tablets will contain excipients including glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. One embodiment provides the formulation as a solid dosage form including a solid oral dosage form. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

[0051] While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations (compositions). The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

[0052] The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with inactive ingredients (e.g., a carrier, pharmaceutical excipient, etc.) which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0053] In certain embodiments, formulations suitable for oral administration are presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient.

[0054] In certain embodiments, the pharmaceutical formulations include one or more compounds of the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or

sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0055] The amount of active ingredient that is combined with the inactive ingredients to produce a dosage form will vary depending upon the host treated and the particular mode of administration. For example, in some embodiments, a dosage form for oral administration to humans contains approximately 1 to 1000 mg of active material formulated with an appropriate and convenient amount of carrier material (e.g., inactive ingredient or excipient material). In certain embodiments, the carrier material varies from about 5 to about 95% of the total compositions (weight: weight). In some embodiments, the pharmaceutical compositions described herein contain about 1 to 800 mg, 1 to 600 mg, 1 to 400 mg, 1 to 200 mg, 1 to 100 mg or 1 to 50 mg of the compound of Formula I, II, III or IV (such as any one of IVa-IVh), or a stereoisomer, or a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical compositions described herein contain not more than about 400 mg of the compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical compositions described herein contain about 100 mg of the compound of Formula IVa-IVh, or a pharmaceutically acceptable salt thereof.

[0056] It should be understood that in addition to the ingredients particularly mentioned above the formulations disclosed herein 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.

[0057] Veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier are further provided.

[0058] Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

[0059] Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses), the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies.

Routes of Administration

[0060] One or more compounds of Formulas IVa-IVh, (herein referred to as the active ingredients), or a pharmaceutically acceptable salt thereof, are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally. Accordingly, in one embodiment, the pharmaceutical compositions described herein are oral dosage forms. In certain embodiments, the pharmaceutical compositions described herein are oral solid dosage forms.

[0061] One skilled in the art will recognize that substituents and other moieties of the compounds of the generic formula herein should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds which have such stability are contemplated as falling within the scope of the present invention. It should be understood by one skilled in the art that any combination of the definitions and substituents described above should not result in an inoperable species or compound.

Combination Therapy

[0062] In yet another embodiment, the present application discloses pharmaceutical compositions comprising a compound of Formulas IVa-IVh, or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent (i.e., active ingredient), and a pharmaceutically acceptable carrier or excipient. In certain embodiments, additional therapeutic agents include additional antiviral agents.

[0063] The additional therapeutic agent used in combination with the compounds described herein includes, without limitation, any agent having a therapeutic effect when used in combination with the compound of the present invention. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, in certain embodiments, the therapeutic agent used in combination with the compounds of Formulas IVa-IVh, include, without limitation, one of more of the following: interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, NS5b inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, nucleoside analogues, and other drugs for treating HCV infection. In some embodiments, the additional therapeutic agents include, without limitation, NS3 protease inhibitors, NS5a inhibitors, and/or NS5b inhibitors. In some embodiments, a pharmaceutical composition including a compound of Formulas IVa-IVh, or a pharmaceutically acceptable salt thereof and one or more of an NS3 protease inhibitor, an NS5a inhibitor, and/or an NS5b inhibitor is provided. In some embodiments, a pharmaceutical composition including a compound of Formulas IVa-IVh, or a pharmaceutically acceptable salt thereof and one or more of an NS5a inhibitor and/or an NS5b inhibitor is provided. In certain embodiments, pharmaceutical compositions is provided which includes a compound of Formulas IVa-IVh, and one or more additional antiviral agents, wherein the additional antiviral agent is not an interferon, ribavirin, or a ribavirin analogue. In further embodiments, pharmaceutical compositions is provided which includes a compound of Formulas IVa-IVh, and one or more additional antiviral agents, wherein the additional antiviral agent is not ribavirin or a ribavirin analogue.

[0064] In certain embodiments, the compounds disclosed herein are combined with one or more other active ingredients (e.g., one or more additional antiviral agents) in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination is administered in two or more administrations. In certain embodiments, the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined pharmaceutical composition; (2) delivered by alternation or in parallel as separate pharmaceutical composition; or (3) by some other regimen. When delivered in alternation therapy, the active ingredients are administered or delivered sequentially, e.g., in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.* serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

[0065] Exemplary interferons include, without limitation, pegylated rIFN-alpha 2b (PEG-Intron), pegylated rIFN-alpha 2a (Pegasys), rIFN-alpha 2b (Intron A), rIFN-alpha 2a (Roferon-A), interferon alpha (MOR-22, OPC-18, Alfaferone, Alfanative, Multiferon, subalin), interferon alfacon-1 (Infergen), interferon alpha-n1 (Wellferon), interferon alpha-n3 (Alferon), interferon-beta (Avonex, DL-8234), interferon-omega (omega DUROS, Biomed 510), albinterferon alpha-2b (Albuferon), IFN alpha XL, BLX-883 (Locteron), DA-3021, glycosylated interferon alpha-2b (AVI-005), PEG-Infergen, PEGylated interferon lambda (PEGylated IL-29), or belerofon, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, and infergen + actimmune.

[0066] Exemplary ribavarin analogs include, without limitation, ribavirin (Rebetol, Copegus), levovirin VX-497, and taribavirin (Viramidine).

[0067] Exemplary NS5A inhibitors include, without limitation, ledipasvir (GS-5885), GS-5816, JNJ-47910382, daclatasvir (BMS-790052), ABT-267, MK-8742, EDP-239, IDX-719, PPI-668, GSK-2336805, ACH-3102, A-831, A-689, AZD-2836 (A-831), AZD-7295 (A-689), and BMS-790052.

[0068] Exemplary NS5B inhibitors include, without limitation, polymerase inhibitor is sofosbuvir (GS-7977), tegobuvir (GS-9190), GS-9669, TMC647055, ABT-333, ABT-072, setrobuvir (ANA-598), filibuvir (PF-868554), VX-222, IDX-375, IDX-184, IDX-102, BI-207127, valopicitabine (NM-283), R1626, PSI-6130 (R1656), PSI-7851, BCX-4678, nesbuvir (HCV-796), BILB 1941, MK-0608, NM-107, R7128, VCH-759, GSK625433, XTL-2125, VCH-916, JTK-652, MK-3281, VBY-708, A848837, GL59728, A-63890, A-48773, A-48547, BC-2329, BMS-791325, and BILB-1941.

[0069] Exemplary NS3 protease inhibitors include, without limitation, GS-9451, GS-9256, simeprevir (TMC-435), ABT-450, boceprevir (SCH-503034), narlaprevir (SCH-900518), vaniprevir (MK-7009), MK-5172, danoprevir (ITMN-191), sovaprevir (ACH-1625), neceprevir (ACH-2684), Telaprevir (VX-950), VX-813, VX-500, faldaprevir (BI-201335), asunaprevir (BMS-650032), BMS-605339, VBY-376, PHX-1766, YH5531, BILN-2065, and BILN-2061.

[0070] Exemplary alpha-glucosidase 1 inhibitors include, without limitation, celgosivir (MX-3253), Miglitol, and UT-231B.

[0071] Exemplary hepatoprotectants include, without limitation, IDN-6556, ME 3738, MitoQ, and LB-84451.

[0072] Exemplary non-nucleoside inhibitors of HCV include, without limitation, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives.

[0073] Exemplary nucleoside analogues include, without limitation, ribavirin, viramidine, levovirin, a L-nucleoside, or isatoribine and said interferon is α-interferon or pegylated interferon.

[0074] Exemplary other drugs for treating HCV infection include, without limitation, imiquimod, 852A, GS-9524, ANA-773, ANA-975, AZD-8848 (DSP-3025), PF-04878691, and SM-360320, cyclophillin inhibitors (e.g., DEBIO-025, SCY-635, or NIM811) or HCV IRES inhibitors (e.g., MCI-067).; emericasan (IDN-6556), ME-3738, GS-9450 (LB-84451), silibilin, or MitoQ. BAS-100, SPI-452, PF-4194477, TMC-41629, GS-9350, GS-9585, and roxythromycin.

[0075] Additional exemplary other drugs for treating HCV infection include, without limitation, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975 (isatoribine), XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811.

[0076] Still further exemplary other drugs for treating HCV infection include, without limitation, thymosin alpha 1 (Zadaxin), nitazoxanide (Alinea, NTZ), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), GS-9525, KRN-7000, civacir, GI-5005, XTL-6865, BIT225, PTX-111, ITX2865, TT-033i, ANA 971, NOV-205, tarvacin, EHC-18, VGX-410C, EMZ-702, AVI 4065, BMS-650032, Bavituximab, MDX-1106 (ONO-4538), Oglufanide, FK-788, VX-497 (merimepodib), DEBIO-025, ANA-975 (isatoribine), XTL-6865, or NIM811.

General Synthetic Procedures

[0077] The schemes, procedures, and examples provided herein describe the synthesis of compounds disclosed herein as well as intermediates used to prepare the compounds. It is to be understood that individual steps described herein may be combined. It is also to be understood that separate batches of a compound may be combined and then carried forth in the next synthetic step.

[0078] The following schemes describe methods that are useful for preparing compounds disclosed herein.

[0079] L_F is a "linker fragment," (*that is to say,* a precursor to L) wherein an attached unsaturated carbon-carbon bond (*e.g.* alkene or alkyne) at the portion of L_F distal to

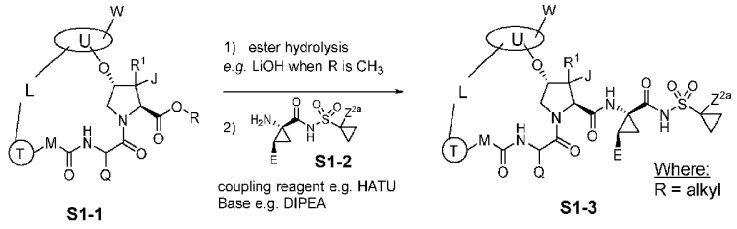
Ⓣ

facilitates, as a non-limiting example, a metal catalyzed reaction that results in the connection of L_F to U to form an L group. Non-limiting examples of metal catalyzed reactions that result in such a connection include Ru catalyzed ring closing metathesis or a Pd catalyzed cross coupling reaction (e.g. Negishi, Heck, or Sonagashira couplings).

[0080] ^1H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: *e.g.* s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations have been used for common solvents used in nuclear magnetic resonance experiments: $CDCl_3$, deuterochloroform; CD_3OD, perdeuteromethanol; CD_3CN, perdeuteroacetonitrile; d_6-DMSO, perdeuterodimethylsulfoxide. Mass spectra were obtained using Thermo Scientific or Agilent Technologies mass spectrometers equipped with electrospray ionisation (ESI). Masses are reported as ratios of mass to charge (*m/z*) of, for example, an ion of the compound (represented by $[M]^+$), an ion formed from the compound with another ion, such as a hydrogen ion (represented by $[M+H]^+$), a sodium ion (represented by $[M+Na]^+$), an ion formed from the compound by losing an ion, such as the deprotonated compound (represented by $[M-H]^-$), etc. Analytical HPLC measurements were performed on Agilent Technologies Series 1100 HPLC using Phenomenex Kinetex C18, 2.6 um 100 A, 4.6 x 100 mm column with an elution program of 2% Solvent B for 0.55 min, gradient to 98% solvent B over 8 min which is maintained at 98% solvent B for 0.40 min before returning to 2% solvent B over 0.02 min and maintaining at 2% solvent B for 2.03 min at a flow rate of 1.5 mL/min (Solvent A = MiliQ filtered H_2O + 0.1% TFA, Solvent B = MeCN + 0.1 % TFA). The term "thin layer chromatography (TLC)" refers to silica gel chromatography using silica gel 60 F_{254} plates. The retention factor ("R_f") of a compound is the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate. Terms such as "early eluting" and "late eluting" refer to the order in which a compound elutes or is recovered from a solid stationary phase/liquid solvent mobile phase based chromatography method (e.g. normal phase silica gel chromatography or reverse phase high pressure liquid chromatography

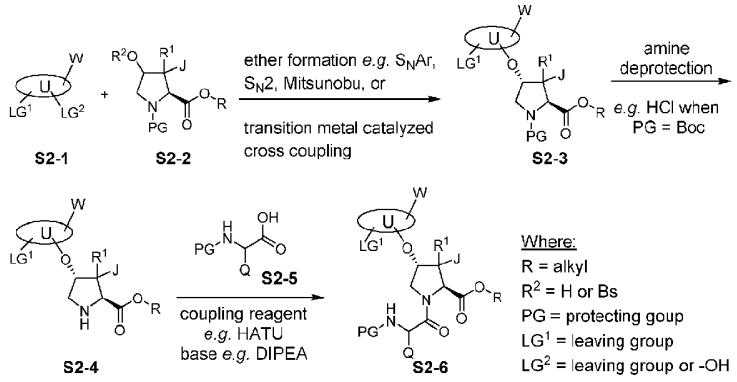
(HPLC)).

Scheme 1



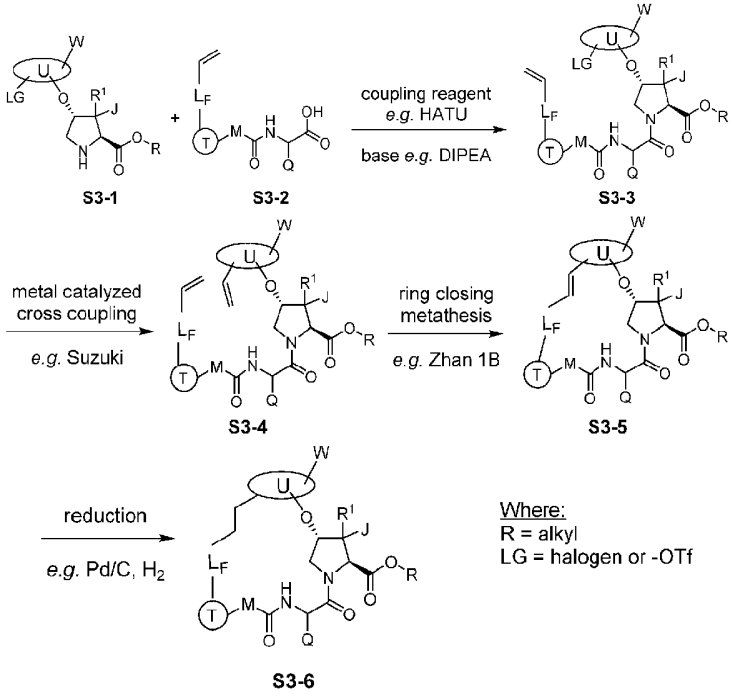
[0081] Scheme 1 demonstrates a general route to **S1-3**, where J, R^1, R, M, L, T, U, W and Q are as defined herein, Z^{2a} is as defined in Formula IV or III, or is H or Z^{2a} as defined in Formula I or II. In scheme 1, ester intermediate **S1-1** is hydrolyzed with a base such as lithium hydroxide when R is C_1-C_3 alkyl (e.g., methyl), or with acid such as trifluoroacetic acid when R is *tert*-butyl. The product of the ester hydrolysis is then coupled to an intermediate **S1-2** through a coupling reaction (e.g. using a peptide coupling agent such as HATU and a base such as DIPEA) to generate compounds of the general structure **S1-3**.

Scheme 2



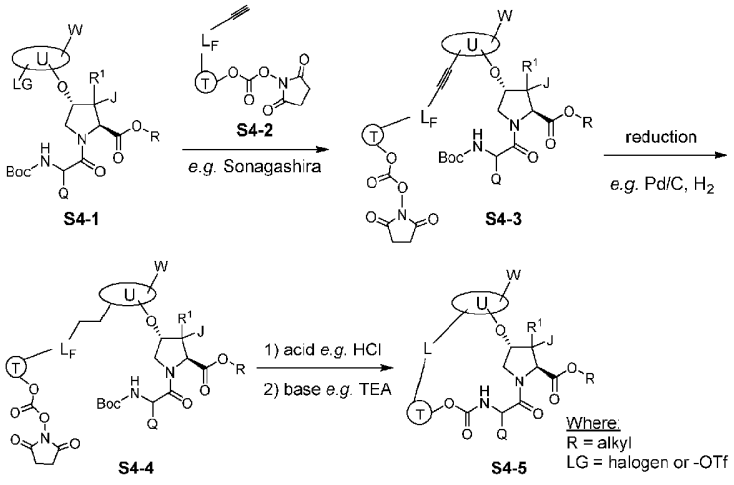
[0082] Scheme 2 shows a general synthesis of an intermediate **S2-6** where U, W, R^1, J, and Q are as defied herein. In scheme 2, an appropriately substituted and protected proline species **S2-2** undergoes an etherification reaction such as S_NAr (*e.g.* treatment with Cs_2CO_3 and **S2-1** where R^2 is H and LG^2 is halogen), S_N2 (*e.g.* preconversion of **S2-2** to a brosylate (R^2 is Bs) followed by treatment with **S2-1** where LG^2 is -OH and base such as DABCO), Mitsunobu reaction (*e.g.* treatment of **S2-2** with DIAD and triphenylphosphine followed by **S2-1** where LG^2 is -OH) or metal catalyzed cross coupling reaction (LG^2 is halogen, R^2 is H) to generate intermediate **S2-3.** Intermediate **S2-3** is deprotected (*e.g.* 4 N HCl in dioxane when PG is Boc) to make intermediate **S2-4.** Amide bond formation *via* activation of the carboxylic acid of **S2-5** using peptide coupling agents or other carboxylic acid activation methods prior to treatment of **S2-4** provides intermediate **S2-6.**

Scheme 3



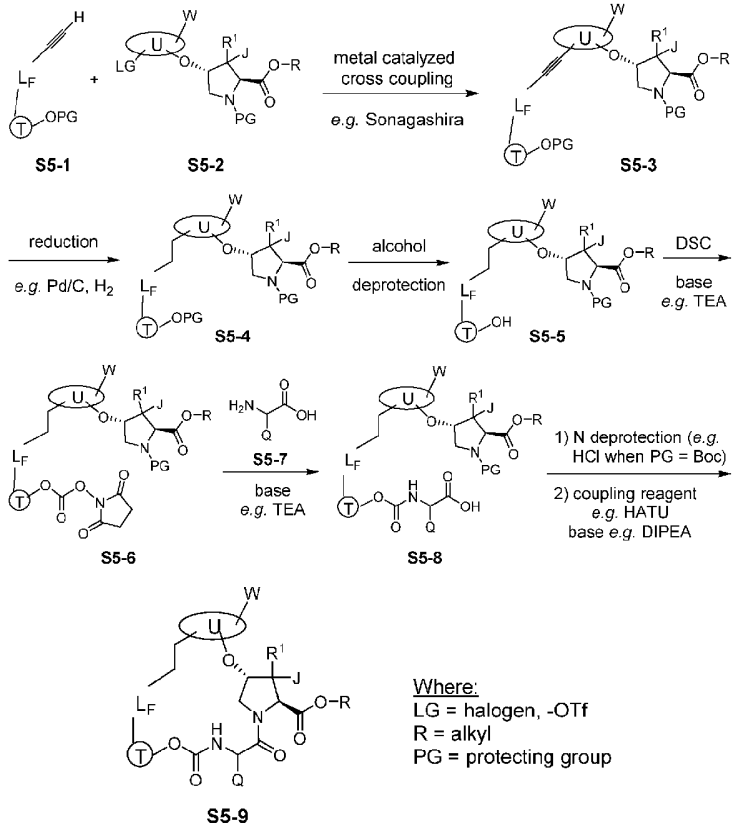
[0083] Scheme 3 shows a general synthesis of intermediate **S3-6** where L_F-CH_2-CH_2 is L, and U, W, R^1, J, Q, M, T, and L are as defied herein. In scheme 3, an intermediate **S3-1** is coupled *via* amide bond formation reaction to an intermediate **S3-2** to provide intermediate **S3-3.** Metal catalyzed cross-coupling (*e.g.* Suzuki reaction using potassium vinyltrifluoroborate, Et_3N, $Pd(dppf)Cl_2$) to give **S3-4,** followed by ring closing metathesis (*e.g.* Zhan 1 B) to give **S3-5,** followed by reduction of the double bond (*e.g.* H_2, 10% Pd/C) provides intermediate **S3-6.**

Scheme 4



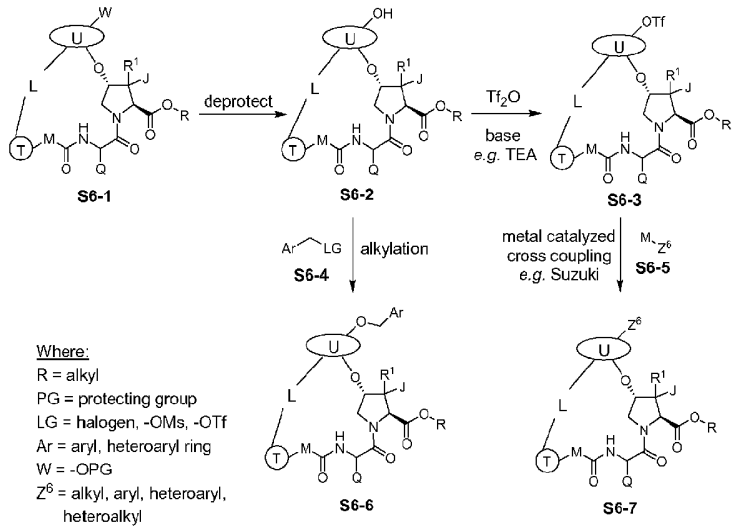
[0084] Scheme 4 shows a general synthesis of an intermediate **S4-5** where L_F-CH_2-CH_2 is L, and U, W, R^1, J, Q, Q and L are as defied herein. In scheme 4, intermediate **S4-1** is protected with a protecting group such as Boc. **S4-1** undergoes a transition metal catalyzed cross coupling (*e.g.* Sonogashira coupling) to an intermediate **S4-2** to provide intermediate **S4-3.** The triple bond of intermediate **S4-3** is reduced to a single bond by hydrogenation (*e.g.* H_2, catalytic 10% Pd/C) to give intermediate **S4-4.** Deprotection of the Boc-amine followed by coupling under basic conditions (*e.g.* triethylamine) provides intermediate **S4-5.**

Scheme 5



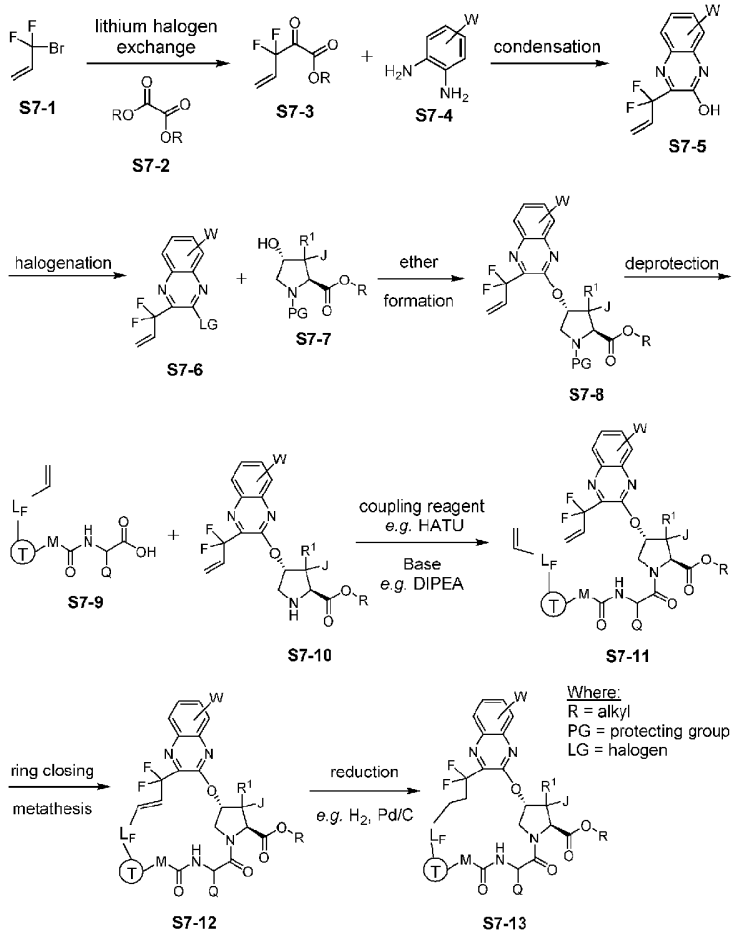
[0085] Scheme 5 shows a general synthesis of an intermediate **S5-9** where L_F-CH_2-CH_2 is L, and U, W, R^1, J, Q, T and L are as defied herein. In scheme 5 intermediate **S5-1** undergoes a metal catalyzed cross coupling (such as Sonogashira reaction) with an intermediate **S5-2** to provide intermediate **S5-3.** The triple bond of intermediate **S5-3** is reduced to a single bond under appropriate conductions such as by hydrogenation (*e.g.* using H_2 over catalytic 10% Pd/C) to give intermediate **S5-4.** Deprotection of the alcohol to provide **S5-5,** followed by activation *(e.g.* DSC under basic conditions, *e.g.* triethylamine) provides intermediate **S5-6.** Coupling of **S5-6** and **S5-7** under basic conditions provides **S5-8.** Deprotection of the proline nitrogen (*e.g.* HCl in dioxane when PG = Boc) followed by a macrolactamization (*e.g.* coupling agent such as HATU under basic conditions) provides intermediate **S5-9.**

Scheme 6



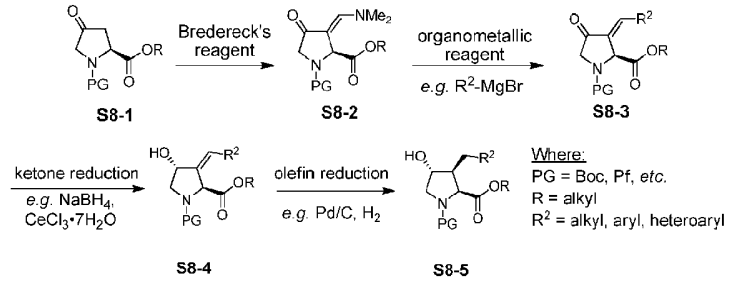
[0086] Scheme 6 shows a general synthesis of the intermediates **S6-6** and **S6-7** where U, R^1, J, Q, M, T and L are as defied herein. In scheme 6 intermediate **S6-1,** W is OPG, where PG is a protecting group. **S6-1** is first deprotected to give intermediate **S6-2.** Alkylation of intermediate **S6-2** with an appropriate electrophile such as **S6-4** provides intermediate **S6-6.** Reaction of **S6-2** with triflic anhydride provides **S6-3,** which then undergoes metal catalyzed cross coupling with an appropriate nucleophilic coupling partner such as **S6-5** (*e.g.* Sonagashira or Suzuki reaction) to provide intermediate **S6-7.**

Scheme 7



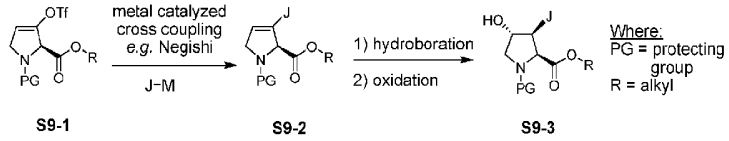
[0087] Scheme 7 shows a general synthesis of intermediate **S7-13** where L_F-CH_2-CH_2-CF_2 is L, and W, R^1, J, Q, M, and T are as defied herein. In **S7-13,** L is C_1-C_3 alkyl. In Scheme 7, intermediate **S7-1** first undergoes lithium halogen exchange and then is treated with intermediate **S7-2** to generate intermediate **S7-3,** which is then condensed with intermediate **S7-4** to provide quinoxaline intermediate **S7-5.** Halogenation of **S7-5** (*e.g.* $POCl_3$) provides intermediate **S7-6.** Intermediate **S7-6** is attached via an ether formation to intermediate **S7-7** through an S_NAr reaction (*e.g.* Cs_2CO_3) to generate intermediate **S7-8.** Deprotection of the N-PG of intermediate **S7-8** provides **S7-10.** An amide bond coupling reaction of intermediate **S7-9** and intermediate **S7-10** (*e.g.* EDC and HOBT, or HATU, NMM, DIPEA) provides intermediate **S7-11.** Ring closing metathesis of **S7-11** generates intermediate **S7-12.** Reduction of the double bond (*e.g.* hydrogenation over palladium on carbon) provides intermediate **S7-13.**

Scheme 8



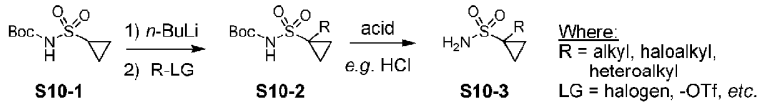
[0088] Scheme 8 shows a general syntheses of intermediate **S8-5** wherein an appropriately protected 4-oxo proline **S8-1** is reacted with Bredereck's reagent to generate enaminone **S8-2.** Addition of an organometallic species provides enone **S8-3,** which undergoes reduction to hydroxyl intermediate **S8-4** in a stereoselective manner (*e.g.* Luche reduction or CBS reduction). Subsequent olefin reduction gives 3-substituted hydroxy proline intermediate **S8-5.**

Scheme 9



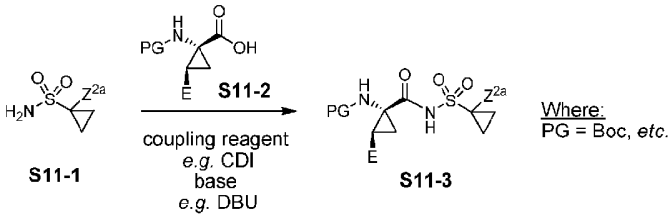
[0089] Scheme 9 shows a general synthesis of intermediate **S9-3** wherein a vinyl triflate **S9-1** (prepared for example, by methods in Kamenecka, T.M., et al. Tetrahedron Letters, 2001, 8571) undergoes metal catalyzed cross coupling *(e.g.* Negishi coupling) to generate intermediate **S9-2.** Hydroboration and subsequent oxidation of intermediate **S9-2** provides intermediate **S9-3.**

Scheme 10



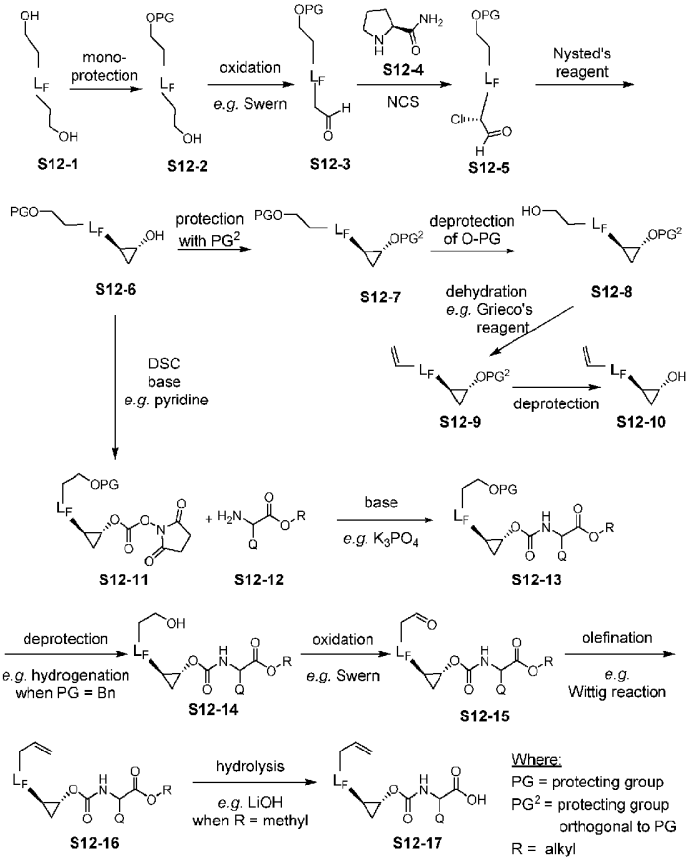
[0090] Scheme 10 shows a general synthesis of substituted sulfonamide intermediate **S10-3.** *Tert*-butyl cyclopropylsulfonylcarbamate **S10-1** is deprotonated (*e.g. n*-BuLi) and reacted with an electrophile *(e.g.* alkyl halide) to give the protected substituted sulfonamide intermediate **S10-2,** which is then deprotected (*e.g.* 4 N HCl in dioxane) to provide intermediate **S10-3.**

Scheme 11



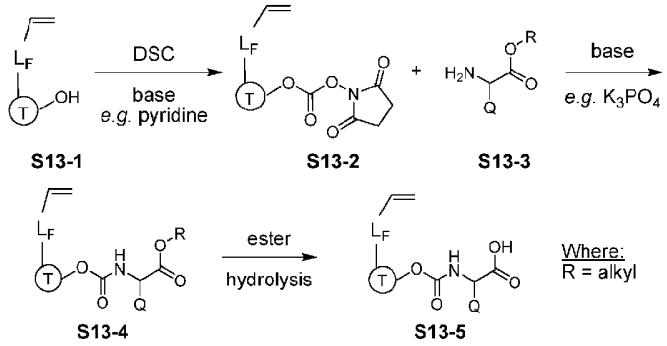
[0091] Scheme 11 shows a general synthesis of an intermediate **S11-3** where E is as defined herein. In Scheme 11, a sulfonamide **S11-1** is coupled to a protected amino acid **S11-**2 using a coupling agent such as CDI and a base such as DBU.

Scheme 12



[0092] Scheme 12 shows a general synthesis of intermediates **S12-10** and **S12-17,** where L_F is C_1-C_3 alkylene. In Scheme 12, both syntheses begin with the monoprotection of intermediate **S12-1** to produce **S12-2,** followed by oxidation (*e.g.* Swern oxidation) to provide intermediate **S12-3.** Enantioselective alpha chlorination (*e.g.* organocatalyst **S12-4** and NCS) provides chloroaldehyde **S12-5.** Reaction of **S12-5** with a bis-zinciomethane derivative (*e.g.* Nysted's reagent) provides cyclopropane intermediate **S12-6.** Intermediate **S12-6** is orthogonally protected to provide intermediate **S12-7.** Deprotection of -OPG of **S12-7** provides intermediate **S12-8,** which is subsequently dehydrated (*e.g.* Grieco's reagent) to intermediate **S12-9** and finally O-PG^2 is removed to afford intermediate **S12-10.** Intermediate **S12-6** is alternatively be activated (*e.g.* DSC and a base such as pyridine) to provide intermediate **S12-11** which is coupled to intermediate **S12-12** to provide carbamate intermediate **S12-13.** Intermediate **S12-13** is deprotected to give intermediate **S12-14,** which is then oxidized (*e.g.* Swern oxidation) to provide aldehyde intermediate **S12-15.** Olefination (*e.g.* Wittig reaction) of intermediate **S12-15** provides intermediate **S12-16.** Ester hydrolysis *(e.g.* LiOH when R is methyl, TFA when R = *tert*-butyl) affords intermediate **S12-17.**

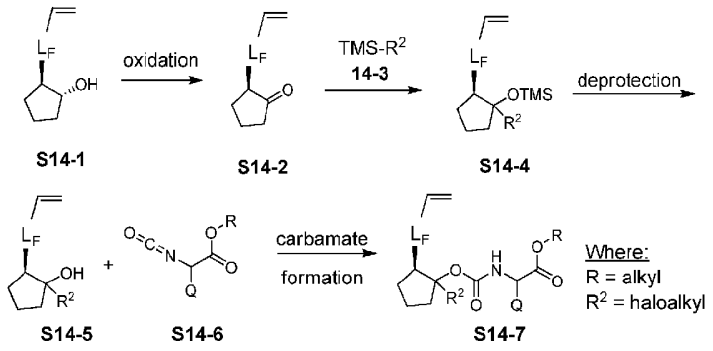
Scheme 13



[0093] Scheme 13 shows a general synthesis of intermediate **S13-5** where Q and T are as defined herein and L_F is C_1-C_3

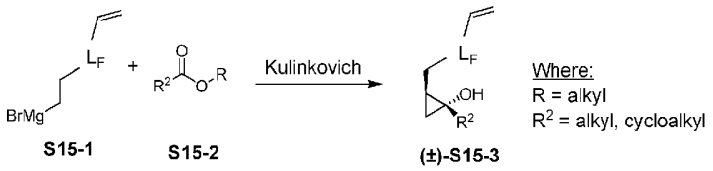
alkylene. Activation of intermediate **S13-1** (*e.g.* DSC) followed by carbamate formation between intermediate **S13-2** and amino acid ester intermediate **S13-3** under basic conditions gives ester intermediate **S13-4.** Ester hydrolysis (*e.g.* LiOH when R = methyl or TFA when R = *tert*-butyl) provides intermediate **S13-5.**

Scheme 14



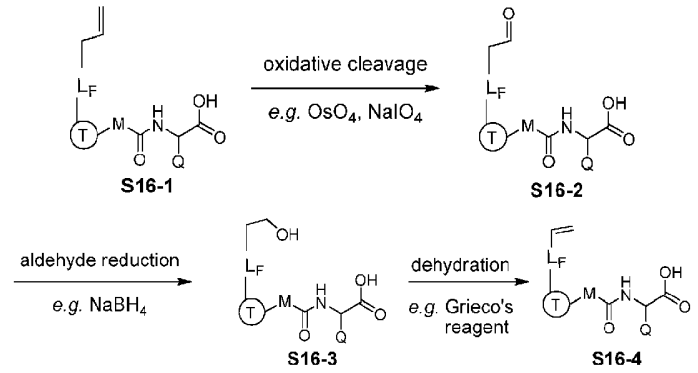
[0094] Scheme 14 shows a general synthesis of intermediate **S14-7** where Q is as defined herein and L_F is C_1-C_3 alkylene. Oxidation of intermediate **S14-1** (e.g. Dess-Martin periodinane) produces ketone **S14-2.** Treatment of **S14-2** with **S14-3** (*e.g.* R^2 is $-CF_3$) in the presence of suitable reagent (such as CsF) provides intermediate **S14-4.** Deprotection of **S14-4** (*e.g.* TBAF) provides **S14-5,** which is then added to an isocyanate **S14-6** to give intermediate **S14-7.**

Scheme 15



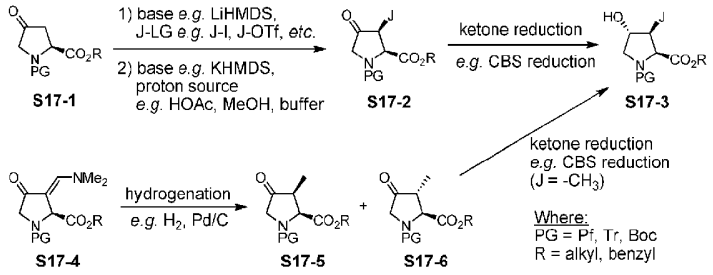
[0095] Scheme 15 shows a general synthesis of an intermediate **(±)-S15-3**, generated from the Kulinkovich reaction of a Grignard reagent **S15-1** and an ester **S15-2,** according to standard procedures as described in Kulinkovich, O.G. and Kananovich, D.G., Eur. J. Org, Chem. 2007, 2007, 2121.

Scheme 16



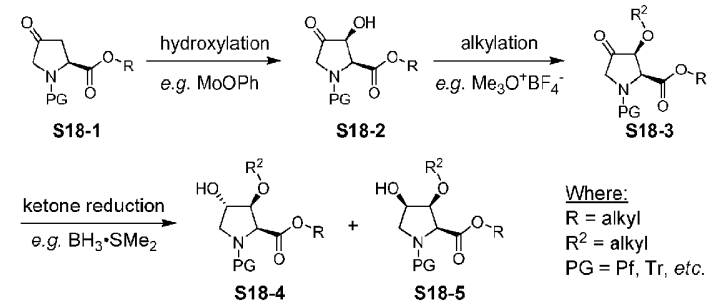
[0096] Scheme 16 shows a general synthesis of an intermediate **S16-4** where Q, M, and T are as defined herein and L_F is C_1-C_3 alkylene. In Scheme 16, olefin **S16-1** undergoes oxidative cleavage (*e.g.* OsO_4, $NaIO_4$) to aldehyde **S16-2,** which is then reduced to alcohol **S16-3** (*e.g.* $NaBH_4$) and finally is dehydrated (*e.g.* Greico elimination) to afford intermediate **S16-4.**

Scheme 17



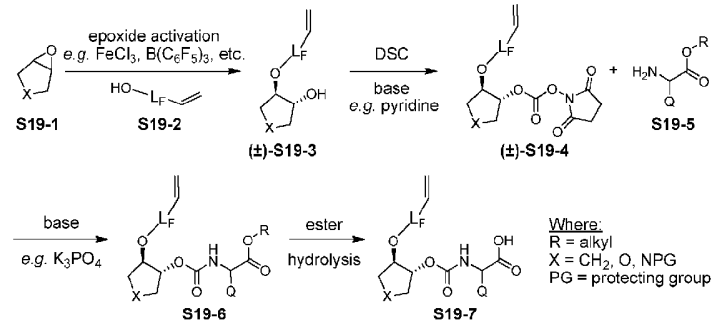
[0097] Scheme 17 shows two general synthetic strategies for producing intermediate **S17-3** where J is as defined herein. In Scheme 17, an appropriately protected 4-oxo proline **S17-1** is deprotonated and alkylated (*e.g.* LiHMDS followed by J-LG). A second deprotonation with base followed by re-protonation at low temperature generates stereoenriched intermediate **S17-2,** based on a described protocol (Blanco, M-J. et. al. J. Org. Chem. 1999, 64, 8786). Reduction of the ketone in a stereoselective manner (*e.g.* CBS reduction) provides alcohol **S17-3.** Where J is methyl, Scheme **17** shows an alternative general synthesis wherein intermediate **S17-4** is hydrogenated to generate a mixture of **S17-5** and **S17-6.** Ketone reduction of **S17-5** in a stereoselective manner (*e.g.* CBS reduction) provides intermediate **S17-3,** where J is methyl.

Scheme 18



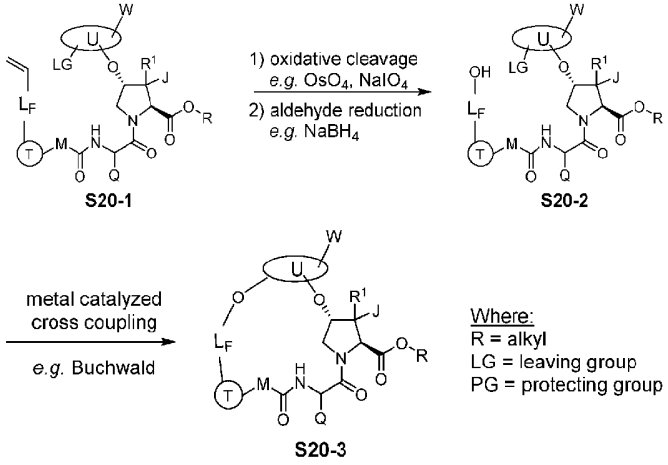
[0098] Scheme 18 shows a general synthesis of intermediates **S18-4** and **S18-5,** wherein an appropriately protected 4-oxo proline **S18-1** is hydroxylated in a stereoselective manner (*e.g.* MoOPh) to provide intermediate **S18-2,** which is subsequently reacted with an alkylating agent (*e.g.* trimethyloxonium tetrafluoroborate) to afford intermediate **S18-3.** Reduction of the ketone (*e.g.* BH_3•SMe_2 complex) provides intermediates **S18-4** and **S18-5.**

Scheme 19



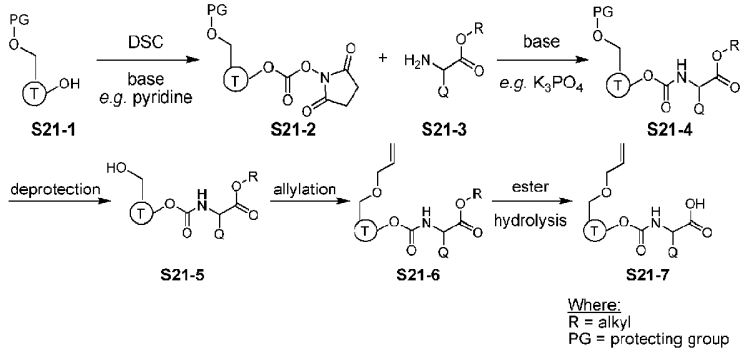
[0099] Scheme 19 shows a general synthesis of an intermediate **S19-7** where Q is as defined herein and L_F is C_1-C_3 alkylene. In Scheme 19, an epoxide intermediate **S19-1** is converted to the (±)-*trans*- intermediate **S19-3.** Activation of the alcohol intermediate **(±)-S19-3** (*e.g.* DSC) produces carbonate **(±)-S19-4,** which is treated with intermediate **S19-5** to afford carbamate intermediate **S19-6.** Intermediate **S19-6** then undergoes ester hydrolysis (*e.g.* LiOH when R = methyl or TFA when R = *tert*-butyl) to provide intermediate **S19-7.**

Scheme 20



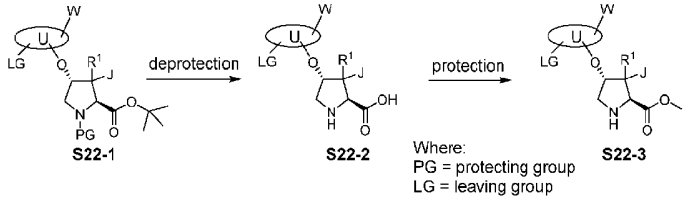
[0100] Scheme 20 shows a general synthesis of an intermediate **S20-3** where L_F-O is F, and U, W, R^1, J, Q, M, T and L are as defied herein. In scheme 20, intermediate **S20-1** first undergoes oxidative cleavage of an olefin (*e.g.* OsO_4, $NaIO_4$ and subsequent reduction of the resultant aldehyde (*e.g.* $NaBH_4$) to provide intermediate **S20-2.** Transition metal catalyzed cross coupling provides intermediate **S20-3.**

Scheme 21



[0101] Scheme 21 shows a general synthesis of an intermediate **S21-7** where Q and T are as defined herein. In Scheme 21, activation of mono-protected diol **S21-1** (*e.g.* DSC) followed by coupling with amino ester intermediate **S21-3** provides carbamate intermediate **S21-4.** Intermediate **S21-4** is then deprotected to unmask the alcohol functionality (intermediate **S21-5**) which is then allylated to provide intermediate **S21-6.** Intermediate **S21-6** then undergoes ester hydrolysis (*e.g.* LiOH when R = methyl or TFA when R = *tert*-butyl) to provide intermediate **S21-7.**

Scheme 22

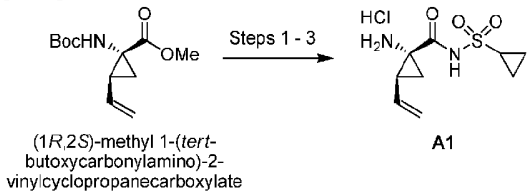


[0102] Scheme 22 shows a general synthesis of an intermediate **S22-3** where U, W, R^1, J, and Q are as defied herein. In scheme 22 intermediate **S22-1** is globally deprotected to provide amino acid intermediate **S22-2.** The acid functionality of intermediate **S22-2** is then converted to a base-labile carboxylic acid ester (*e.g.* methyl ester), intermediate **S22-3.**

Preparation of Selected Intermediates

Preparation of Intermediate A1.

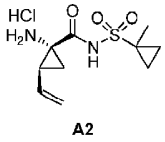
[0103]



[0104] Steps 1-3. Preparation of Intermediate **A1:** Intermediate **A1** was prepared using the procedure detailed in Example 2.12 of International Patent Publication No. WO 2008/064066 (hereinafter "WO '066") (p. 75-76) substituting (1 R,2S)-methyl 1-(tert-butoxycarbonylamino)-2-vinylcyclopropane-carboxylate (prepared according to Beaulieu, P.L., et al., J. Org. Chem. 2005, 70, 5869) for (1 R,2S)-ethyl 1-(tert-butoxycarbonylam ino)-2-vinylcyclopropane-carboxylate.

Preparation of Intermediate A2.

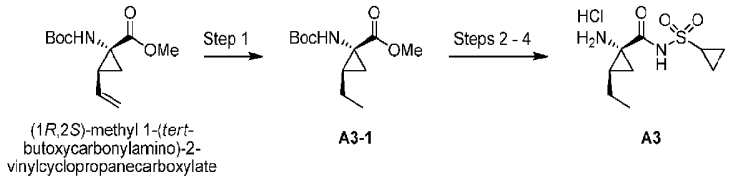
[0105]



[0106] Intermediate **A2** was prepared similarly to Intermediate **A1,** substituting 1-methylcyclopropane-1-sulfonamide (prepared according to Example 1.2 of WO '066, p. 47) for cyclopropanesulfonamide.

Preparation of Intermediate A3.

[0107]

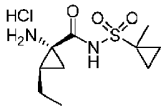


Step 1. Preparation of **A3-1:** Cyclopropane ester **A3-1** was prepared from (1R,2S)-methyl 1-(tert-butoxycarbonylamino)-2-vinylcyclopropanecarboxylate (prepared according to Beaulieu, P.L., et al., J. Org. Chem. 2005, 70, 5869) using the procedure detailed in Example 26 of International Patent Publication No. WO 2009/005677 (hereinafter "WO '677") (p. 176).

Steps 2-4. Preparation of Intermediate **A3:** Intermediate **A3** was prepared similarly to (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropanecarbox-amide hydrochloride of Example 2.12 of WO '066 (p. 75-76) substituting **A3-1** for (1R,2S)-ethyl 1-(tert-butoxycarbonylamino)-2-vinylcyclopropane-carboxylate.

Preparation of Intermediate A4.

[0108]



A4

[0109] Intermediate **A4** was prepared similarly to Intermediate **A3,** substituting 1-methylcyclopropane-1-sulfonamide (prepared according to Example 1.2 of WO '066, p. 47) for cyclopropanesulfonamide.

Preparation of Intermediate A5.

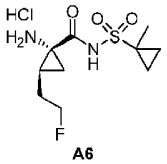
[0110]

A5-1 A5

[0111] Steps 1-3. Preparation of Intermediate **A5:** Intermediate **A5** was prepared similarly to (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropane-carboxamide hydrochloride of Example 2.12 of WO '066 (p. 75-76) substituting **A5-1** (prepared according to Example 104 of WO '677, p. 265) for (1 R,2S)-ethyl 1-(tert-butoxycarbonylam ino)-2-vinylcyclopropanecarboxylate.

Preparation of Intermediate A6.

[0112]

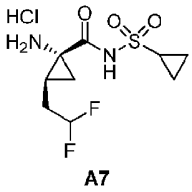


A6

[0113] Intermediate **A6** was prepared similarly to Intermediate **A5,** substituting 1-methylcyclopropane-1-sulfonamide (prepared according to Example 1.2 of WO '066, p. 47) for cyclopropanesulfonamide.

Preparation of Intermediate A7.

[0114]

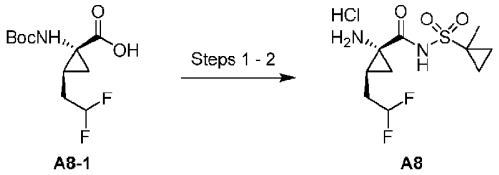


A7

[0115] Intermediate **A7** was prepared according to Example 97.1.6 of U.S. Patent Publication No. 2009/274652 (hereinafter "US '652"), p. 72-73.

Preparation of Intermediate A8.

[0116]

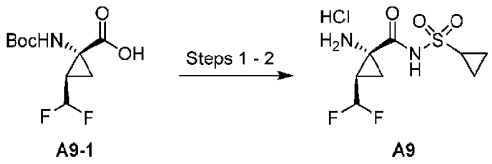


A8-1 A8

[0117] Steps 1-2. Preparation of Intermediate **A8:** Intermediate **A8** was prepared similarly to (1 R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropane-carboxamide hydrochloride of Example 2.12 of WO '066 (p. 75-76) substituting **A8-1** (prepared according to the procedure detailed in Example 97.1.4 of US '652, p. 72-3) for (1 R,2S)-1-(tert-butoxycarbonylamino)-2-vinylcyclo-propanecarboxylic acid and substituting 1-methylcyclopropane-1-sulfonamide (prepared according to Example 1.2 of WO `066, p. 47) for cyclopropanesulfonamide. **A8-1** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (br s, 1 H), 6.05 - 5.75 (m, 1 H), 5.38 (br s,1H), 2.04 (m, 2H), 1.68 (m, 2H), 1.61 (m, 3H), 1.52 (m, 9H), 1.42 (m, 1 H), 1.28 (m, 1 H), 0.85 (m, 2H).

Preparation of Intermediate A9.

[0118]

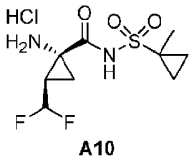


A9-1 A9

[0119] Step 1-2. Preparation of Intermediate **A9:** Intermediate **A9** was prepared similarly to (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropane-carboxamide hydrochloride of Example 2.12 of WO '066 (p. 75-76) substituting **A9-1** (prepared according to Example 1, Steps 1L-1O of International Patent Publication No. WO 2009/134987, p. 75-77) for (1R,2S)-1-(tert-butoxycarbonylamino)-2-vinylcyclopropanecarboxylic acid.

Preparation of Intermediate A10.

[0120]

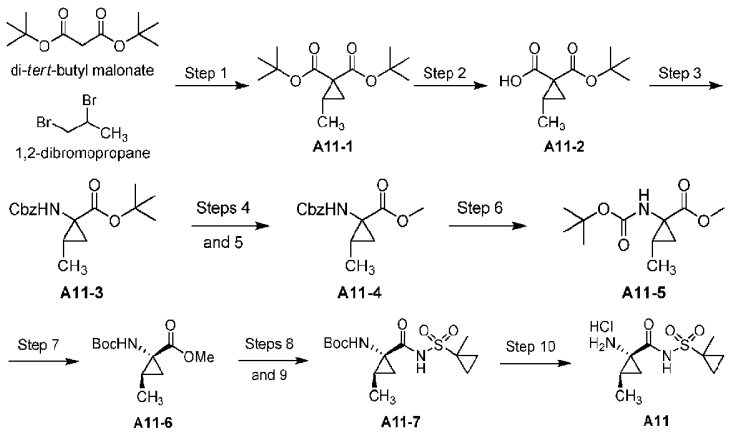


A10

[0121] Intermediate **A10** was prepared similarly to Intermediate **A9,** substituting 1-methylcyclopropane-1-sulfonamide (prepared according to Example 1.2 of WO '066, p. 47) for cyclopropanesulfonamide.

Preparation of Intermediate A11.

[0122]



Step 1. Preparation of **A11-1:** To a solution of NaOH (46.2 g, 50% w/w in water) at rt was added $BnEt_3NCl$ (10.5 g, 46 mmol), di-*tert*-butyl malonate (10 g, 46 mmol) and 1,2-dibromopropane (14 g, 69.3 mmol). The mixture was stirred at rt overnight and was extracted with DCM (3×100 mL). The organic layers were washed with water (80 mL) and brine (50 mL), dried over anhydrous Na_2SO_4. Concentration *in vacuo* produced **A11-1** that was used subsequently without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 1.83-1.62 (m, 1 H); 1.42 (s, 9H); 1.40 (s, 9H); 1.24-1.05 (m, 2H); 1.03-1.02 (d, 3H).

Step 2. Preparation of **A11-2:** To a mixture of *t*-BuOK (175 g, 1.56 mol) in ether (1.2 L) at 0 °C was added water (3.4 mL) followed by addition of diester **A11-1** (91 g, 0.35 mol). The mixture was stirred at rt for three days, then quenched with ice-water. The aqueous layer was extracted with ether (2×400 mL), acidified with critic acid, and then extracted with EA (3×400 mL). The combined ethyl acetate extracts were washed with water (2×100 mL), brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to produce **A11-2** that was used subsequently without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1 H); 1.70-1.64 (s, 1 H); 1.37 (s, 9H); 1.19-1.13 (m, 1 H); 1.03-1.00 (m, 4H). Step 3. Preparation of **A11-3:** To a mixture **A11-2** (33.5 g, 0.17 mol) and triethylamine (70 mL) in THF (200 mL) at 0 °C was added ethyl chloroformate (22 mL). The mixture was stirred at 0 °C for 1 h. To the mixture at 0 °C was added sodium azide (54 g, 0.83 mol, 4.9 eq) in water (100 mL), the mixture was stirred for 40 min. The mixture was extracted with EA (2×400 mL), washed with water (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to produce a residue that was taken up in toluene (100 mL) and treated with benzyl alcohol (50 mL). The mixture was then heated at 70°C for 2 h, cooled to rt, adjusted to pH 8 with sodium bicarbonate, and then extracted with ether (3×200 mL). The aqueous layer was then adjusted to pH 5 with 1 N HCl and extracted with EA (2×300 mL). The combined ethyl acetate extracts were washed with water (100 mL), brine (80 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give CBZ protected amine **A11-3** (16 g) that is used subsequently without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 1 H); 7.28-7.15 (m, 5H); 4.97-5.03 (m, 2H); 1.33 (s, 9H); 1.33-1.17 (m, 2H); 1.10 (d, J = 6.8 Hz, 3H); 0.90-1.00 (m, 1 H).

Steps 4 and 5. Preparation of **A11-4:** To a solution of Cbz protected amine **A11-3** (16 g, 52 mmol) in DCM (250 mL) was added dropwise TFA (250 mL, 3.24 mol) at rt and the mixture stirred at rt overnight. The mixture was concentrated *in vacuo,* adjusted to pH 8~9 using aqueous sodium carbonate and washed with ether (3×80 mL). The aqueous phase was then adjusted to pH 5~6 using 1 N HCl and extracted with EA (2×300 mL). The combined ethyl acetate phases were washed with water (80 mL), brine (80 mL), dried over anhydrous Na_2SO_4 and concentrated to give 13 g as a slightly yellow oil that was used in the next step without further purification. This material (8.0 g, 32 mmol) was taken up in methanol (200 mL), treated with thionyl chloride (15 mL) at 0 °C, then stirred at rt overnight. The resulting mixture was concentrated *in vacuo* and purified by flash chromatography on silica (eluent PE/EA 10:1-5:1) to give methyl ester **A11-4** (6 g). ^1H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 1 H); 7.37-7.26 (m, 5H); 4.99 (s, 2H); 3.61 (s, 3H); 1.48-1.45 (m, 1 H); 1.17-1.08 (m, 2H); 1.06-1.04 (d, 3H).

Step 6. Preparation of **A11-5:** Cbz carboxamide **A11-4** (36 g, 0.15 mol), Boc_2O (40 g, 0.18 mol), and Pd/C (3.6 g, 10% w/w) were combined in methanol under H_2 and stirred at 32°C overnight. The reaction mixture was filtered to remove the catalyst, additional Boc_2O (40 g, 0.18 mol) and Pd/C (3.6 g, 10% w/w) were added and the reaction placed under a H_2 atmosphere with stirring at rt for a weekend. The reaction mixture was filtered to remove the catalyst, concentrated *in vacuo* and purified by flash chromatography on silica (eluent PE/EA 20:1-10:1) to produce Boc protected amine **A11-5.** ^1H NMR (400 MHz, DMSO-d_6) δ 7.48 (s, 1H), 3.59 (s, 3H), 1.43-1.41 (m, 1H), 1.34 (s, 9H), 1.21-1.18 (m, 1H), 1.07-1.01 (m,4H).

Step 7. Preparation of **A11-6:** To a solution of NaH_2PO_4 (1.9 g) in water (160 mL) at 40°C was added Alcalase (2.4 U/g, 16 mL).

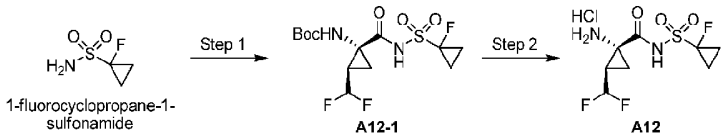
The mixture was adjusted with 50% aqueous sodium hydroxide to pH 8. **A11-5** (2.80 g) in DMSO (32 mL) was added to the buffer dropwise over 30 min. The mixture was stirred at 40 °C and maintained at pH 8 with addition of 50% NaOH for 19 h. The mixture was cooled to rt, with ether (3 x 100 mL) and the organic phase washed with sat. $NaHCO_3$ (2 x 40 mL), water (2 x 40 mL), brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to produce **A11-6.** **^{1}H NMR** (300 MHz, DMSO-d_6) δ 5.18 (br s, 1 H); 3.71 (s, 3H); 1.43-1.18 (m, 2H); 1.34 (s, 9H); 1.07-1.01 (m, 4H). Analysis of the product using chromegaChiral CC3 column (0.46 cm I.D. X 25 cm L, 3 µL injection, 80/20 hexane/IPA, 1 mL/min, 34 °C, 220 nM UV detection) determined the enantiomeric excess was 99.4% (desired RT = 5.238 min, undesired RT = 6.745 min).

Steps 8 and 9. Preparation of **A11-7:** Solid LiOH•H_2O (19.1 g, 455 mmol) is taken up in 50 mL MeOH/50 mL water at rt. Once all LiOH has dissolved, methyl ester **A11-6** (10.4 g, 45.5 mmol) is taken up in 100 mL THF added to reaction mixture and stirred vigorously overnight. The resulting solution is diluted with water (150 mL), adjusted to pH ~ 3 with 12 M HCl and extracted with EtOAc. The combined organic layers are washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to produce a fine white powder (9.2 g). This material (1.5 g, 7 mmol) is taken up in THF (30 mL) and treated with CDI (1.47 g, 9.1 mmol). The resulting solution was heated to 65 °C for 2 h, cooled to rt and treated with DBU (2.1 mL, 13.9 mmol) and 1-methylcyclopropane-1-sulfonamide (1.4 g, 10.5 mmol). The resulting solution is stirred at rt overnight. Addition of 1 M HCl is used to adjust the pH ~ 1 prior to removing the majority of THF *in vacuo*. The resulting slurry is extracted with EtOAc and the combined organics washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to produce 2.29 g of acyl sulfonamide **A11-7.** LCMS-ESI$^+$ (*m/z*): $[M+Na]^+$calcd for $C_{14}H_{24}N_2NaO_5S$: 355.41; found: 355.84.

Step 10. Preparation of Intermediate **A11.** Acyl sulfonamide **A11-7** (0.25 g, 0.75 mmol) in dioxane (1 mL) is treated with HCl (4 M in dioxane, 2.8 mL, 11.2 mmol) at rt. After 4 h, the reaction is concentrated *in vacuo* to produce 0.20 g of Intermediate **A-11** that is used subsequently without additional purification. ^{1}H NMR (400 MHz, CD_3OD) δ 1.87-1.84 (m, 0.5 H); 1.77-1.65 (m, 1.5H); 1.58-1.46 (m, 2H); 1.54 (d, J = 8 Hz, 3H); 1.34-1.26 (m, 3+1 H); 1.02-0.92 (m, 1 H); 0.83-0.77 (m, 1 H).

Preparation of Intermediate A12.

[0123]



1-fluorocyclopropane-1-sulfonamide

A12-1

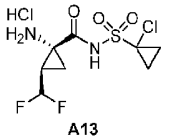
A12

Step 1. Preparation of **A12-1:** A vessel containing a solution of carboxylic acid **A9-1** (1 g, 4 mmol) in THF (15 mL) was treated with CDI (0.84 g, 5.2 mmol), sealed and heated to 75 °C for 2 h. The clear tan colored solution is divided in half and used subsequently without further purification for the remainder of Step 1 in the preparation of Intermediate **A12** as well as the preparation of Intermediate **A13** as detailed below. This solution is treated with 1-fluorocyclopropane-1-sulfonamide (0.42 g, 3 mmol; prepared according to Steps 1, 4, and 9 of Example 7 of International Patent Publication No. WO 2009/14730, p. 107-110) and DBU (0.6 mL, 4 mmol) and allowed to stir overnight at rt. The solution was acidified to pH ~1 with 1 M HCl and concentrated *in vacuo* to remove the majority of THF. The aqueous layer was extracted with EtOAc and the combined organics washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to dryness to afford 0.73 g of the **A12-1** that was used without further purification.

Step 2. Preparation of Intermediate **A12:** Acyl sulfonamide **A12-1** (0.25 g, 0.67 mmol) was taken up in 1 mL dioxane and treated with HCl (4 M in dioxane, 2.5 mL, 11 mmol). The reaction was stirred at rt for 2 h and concentrated *in vacuo* to dryness to afford a quantitative yield of Intermediate **A12.** ^{1}H NMR (400 MHz, CD_3OD) δ 6.04 (td, J_{H-F} = 55.6 Hz, J = 5.2 Hz, 1 H); 2.25-2.14 (m, 1 H); 1.78-1.62 (m, 2H);1.52-1.38 (m, 4H).

Preparation of Intermediate A13.

[0124]

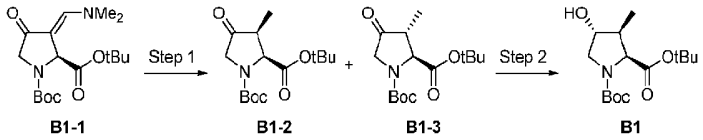


A13

[0125] Intermediate **A13** was prepared similarly to Intermediate **A12,** substituting 1-chlorocyclopropane-1-sulfonamide (prepared according to Li, J, etal. Synlett, 2006, 5, pp. 725-728) for 1-chlorocyclopropane-1-sulfonamide in Step 1. ^{1}H NMR (400 MHz, CD_3OD) δ 6.03 (td, J_{H-F} = 54.8 Hz, J = 6 Hz, 1 H); 2.32-2.18 (m, 1 H); 2.06-1.92 (m, 2H);1.80-1.68 (m, 2+1 H); 1.56-1.44 (m, 1 H); 1.44-1.37 (m, 1 H).

Preparation of Intermediate B1.

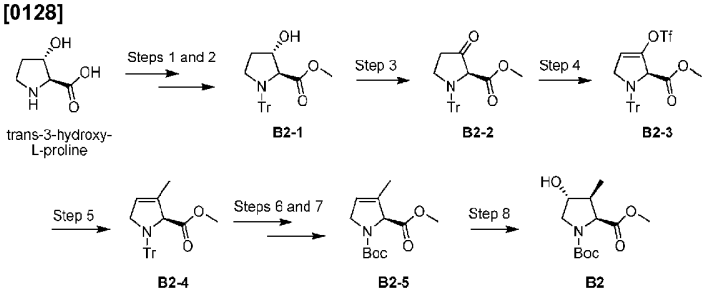
[0126]



[0127] Steps 1 and 2. Preparation of Intermediate **B1:** Enaminone **B1-1** (4.0 g, 11.8 mmol, prepared according to Camplo, M., et al. Tetrahedron 2005, 61, 3725) was dissolved in acetone (120 mL) and the reaction vessel was purged with Ar. Pd/C (10 wt. % Pd, 820 mg) was added in a single portion and the reaction vessel was purged twice with H_2. The reaction was stirred under 1 atm H_2 at rt for 15 h and was then filtered through a pad of Celite with acetone. The filtrate was concentrated and filtered through a plug of silica gel with 30% EtOAc in hexanes to afford a ~2:1 mixture of ketones **B1-2** and **B1-3** (3.48 g) as a white solid. This mixture (3.37 g, 11.3 mmol) was dissolved in THF (100 mL) under Ar. A 1 M solution of (*R*)-(+)-2-methyl-CBS-oxazaborolidine in toluene (11.3 mL, 11.3 mmol) was added in a single portion and the resulting solution was cooled to - 78 °C. A 1 M solution of BH_3•SMe_2 in CH_2Cl_2 (11.3 mL) was then added dropwise over 5 min. The resulting solution was stirred for 20 min and was removed from the cold bath. After an additional 15 min, the reaction was placed in a water bath at ambient temperature. After an additional 7 min, the reaction was quenched by dropwise addition of MeOH (20 mL). After stirring an additional 2.5 h, the reaction mixture was concentrated, dissolved in EtOAc (300 mL), and washed with 0.2 M HCl (200 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (100 mL). The combined organic phase was filtered to remove solids, dried over Na_2SO_4, filtered, and concentrated. The crude residue was dissolved in CH_2Cl_2 and was concentrated onto 20 g silica gel. Purification by silica gel chromatography (25 to 40% EtOAc in hexanes) provided partial separation of Intermediate **B1** from other diastereomeric products. Mixed fractions were pooled and concentrated onto 9 g silica gel. Purification by silica gel chromatography provided Intermediate **B1** contaminated with minor diastereomeric components as a white solid (1.96 g). ^{1}H NMR (400 MHz, $CDCl_3$, rotamers observed) δ 4.25 - 4.15 (m, 1 H), 4.13 - 4.04 (m, 1 H), 3.91 - 3.79 (m, 1 H), 3.28 - 3.09 (m, 1 H), 2.41 - 2.23 (m, 1 H), 2.04 (bs, 1 H), 1.51 - 1.39 (m, 18H), 1.09 - 1.01 (m, 3H).

Preparation of Intermediate B2.

[0128]



Steps 1 and 2. Preparation of **B2-1:** *trans*-3-Hydroxy-L-proline (571 mg, 4.35 mmol, Chem-Impex International, Inc.) was suspended in MeOH and cooled to 0 °C. Thionyl chloride (1.6 mL, 22 mmol) was added over 5 min and the solution was warmed

to rt. After stirring for 24 h, the reaction mixture was concentrated under reduced pressure to afford the methyl ester, which was carried on without further purification. The crude ester was suspended in DCM (22 mL) and treated with TEA (1.3 mL, 9.57 mmol). The stirred mixture was cooled to 0 °C and trityl chloride (1.21 g, 4.35 mmol) was added. The reaction mixture was allowed to gradually come to rt o/n, and then poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted three times with DCM. The combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (25% to 50% EtOAc/Hex to afford alcohol **B2-1** (1.27 g).

Step 3. Preparation of **B2-2:** Alcohol **B2-1** (1.23 g, 3.18 mmol) and 2 g 4 A MS were suspended in DCM (16 mL) and treated with NMO (560 mg, 4.78 mmol) and TPAP (76 mg, 0.218 mmol). After stirring for 30 min, the mixture was filtered over a short pad of silica and eluted off with 50% EtOAc/Hex. The filtrate was concentrated and the crude residue was purified by silica gel chromatography (10% to 30% EtOAc/Hex to afford ketone **B2-2** (0.99 g).

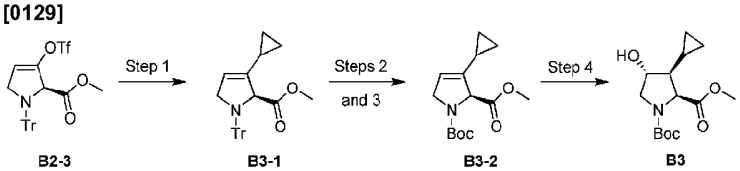
Step 4. Preparation of **B2-3:** LiHMDS (1.0 M in THF, 5.8 mL, 5.8 mmol) was added to THF (22 mL) and the stirred solution was cooled to -78 °C. A rt solution of ketone **B2-2** (2.14 g, 5.55 mmol) in THF (6 mL) was added dropwise by cannula over 5 min. The flask that had contained **B2-2** was then rinsed with THF (4 mL) and the rinsing was added dropwise by cannula to the reaction mixture. After 35 min, *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide) (2.40 g, 6.11 mmol) in THF (6 mL) was added to the reaction mixture dropwise by syringe over 5 min. After another 1 h, the reaction mixture was warmed to rt. Following an additional 30 min, the reaction was quenched by addition of 20 mL H_2O and diluted with Et_2O. The organic solution was washed with 10% NaOH and dried over K_2CO_3, filtered and concentrated under reduced pressure. The crude residue was loaded onto a silica column that had been pre-equilibrated with 1% TEA/Hex. The material was purified by silica gel chromatography (0% to 15% EtOAc/Hex doped with 1 % TEA) to afford enol triflate **B2-3** (1.89 g).

Step 5. Preparation of **B2-4:** Enol triflate **B2-3** (957 mg, 1.85 mmol) was dissolved in THF (9 mL) and treated with $Pd(PPh_3)_4$ (107 mg, 0.0925 mmol) and dimethyl zinc (2.0 M in PhMe, 1.9 mL, 3.7 mmol). The reaction mixture was stirred at rt for 5 h, then more dimethyl zinc (2.0 M in PhMe, 1.9 mL, 3.7 mmol) was added and the reaction was heated to 50 °C for 15 min. After cooling to rt, the mixture was diluted with Et_2O. The organic solution was washed with 10% NaOH twice, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude **B2-4** residue was carried on without further purification. Steps 6 and 7. Preparation of **B2-5:** Compound **B2-4** (1.85 mmol theoretical) was dissolved in 1:1 MeOH/DCM (20 mL) and treated with HCl (4.0 M in dioxane, 2 mL, 8.0 mmol). After stirring for 2 h at rt, the reaction mixture was concentrated and the crude material was carried on without further purification. The crude product amine hydrochloride was treated with Boc_2O (2.02 g, 9.25 mmol), DCM (18 mL), MeOH (1.8 mL) and TEA (0.52 mL, 3.7 mmol). After stirring for 2 h at rt, the reaction mixture was diluted with EtOAc and washed with 10% HCl, saturated aqueous $NaHCO_3$ and brine. The organic solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (15% to 40% EtOAc/Hex) to afford carbamate **B2-5** (331 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{20}NO_4$: 242.14; found: 243.26.

Step 8. Preparation of Intermediate **B2:** Carbamate **B2-5** (345 mg, 1.43 mmol) was dissolved in THF (7 mL) and cooled to 0 °C. BH_3•SMe_2 complex (2.0 M in THF, 0.79 mL, 1.58 mmol) was added dropwise and the reaction mixture was allowed to come to rt gradually. After 15 h, the reaction was quenched by dropwise addition of H_2O (added until bubbling ceased), then cooled to 0 °C. Hydrogen peroxide (30% w/w in H_2O, 0.73 mL, 7.2 mmol) and NaOH (2.0 M in H_2O, 0.86 mL, 1.72 mmol) were added in quick succession and the stirred mixture was heated to 50°C for 35 min. The mixture was then diluted with Et_2O and washed successively with H_2O, saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. Intermediate **B2** was used in subsequent reactions without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{22}NO_5$: 260.15; found: 259.99.

Preparation of Intermediate B3.

[0129]



B2-3 **B3-1** **B3-2** **B3**

Step 1. Preparation of **B3-1:** Enol triflate **B2-3** (91 mg, 0.176 mmol) was dissolved in THF (1.7 mL) and treated with cyclopropyl

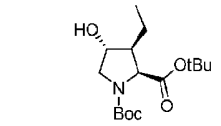
zinc bromide (0.5 M in THF, 1.7 mL, 0.85 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.018 mmol). The stirred reaction mixture was heated to 50 °C for 2 h then cooled to rt and diluted with EtOAc. The organic solution was washed successively with saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (0% to 20% EtOAc/Hex) to afford cyclopropane **B3-1** (43 mg). LCMS-ESI$^+$ (m/z): $[M\text{-}Tr+H]^+$calcd for $C_9H_{14}NO_2$: 168.10; found: 168.04.

Steps 2 and 3. Preparation of **B3-2:** Vinyl cyclopropane **B3-1** (43 mg, 0.11 mmol) was dissolved in 1:1 MeOH/DCM (10 mL) and treated with HCl (4.0 M in dioxane, 1 mL, 4.0 mmol). After stirring for 1.5 h at rt, the reaction mixture was concentrated and the crude material was carried on without further purification. The crude product of step 2 was treated with Boc_2O (229 mg, 1.05 mmol), DMAP (13 mg, 0.105 mmol), DCM (5 mL) and TEA (0.293 mL, 2.10 mmol). After stirring for 5 h at rt, the reaction mixture was diluted with EtOAc and washed with 10% HCl, saturated aqueous $NaHCO_3$ twice and brine. The organic solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10% to 30% EtOAc/Hex) to afford carbamate **B3-2** (20 mg). LCMS-ESI$^+$ (*m/z*): $[M\text{-}(t\text{-}Bu)+H]^+$calcd for $C_{10}H_{14}NO_4$: 212.09; found: 211.91.

Step 4. Preparation of Intermediate **B3:** Carbamate **B3-2** (152 mg, 0.569 mmol) was dissolved in THF (5.7 mL) and cooled to 0 °C. BH_3•SMe_2 complex (2.0 M in THF, 0.31 mL, 0.63 mmol) was added dropwise and the reaction mixture was allowed to come to rt gradually. After 20 h, the reaction was quenched by dropwise addition of H_2O (added until bubbling ceased), then cooled to 0 °C. Hydrogen peroxide (30% w/w in H_2O, 0.29 mL, 2.85 mmol) and NaOH (2.0 M in H_2O, 0.43 mL, 0.86 mmol) were added in quick succession and the stirred mixture was heated to 50 °C for 30 min. The mixture was then diluted with Et_2O and washed successively with H_2O, saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. Intermediate **B3** was carried on without further purification. LCMS-ESI$^+$ (*m/z*): $[M\text{-}(t\text{-}Bu)+H]^+$ calcd for $C_{10}H_{16}NO_5$: 230.10; found: 230.03.

Preparation of Intermediate B4.

[0130]



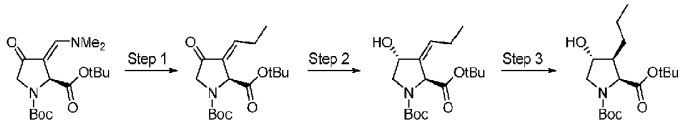
(2*S*,3*S*,4*R*)-di-*tert*-butyl 3-ethyl-4-hydroxypyrrolidine-1,2-dicarboxylate

B4

[0131] Intermediate **B4** ((2S,3S,4R)-di-tert-butyl 3-ethyl-4-hydroxypyrrolidine-1,2-dicarboxylate) was prepared according to Campo, M., et al. Tetrahedron 2005, 61, 3725.

Preparation of Intermediate B5.

[0132]



B1-1 **B5-1** **B5-2** **B5**

Step 1. Preparation of enone **B5-2:** To a solution of **B1-1** in tetrahydrofuran (7.35 mL) was added ethylmagnesium bromide (3 M in diethyl ether, 1.47 mL 4.41 mmol) via syringe at -78 °C under an argon atmosphere. After 2.5 h, the reaction mixture was allowed to warm to rt over 30 min at which point the reaction mixture was diluted with saturated aqueous ammonium chloride solution (20 mL). The resulting mixture was extracted with ethyl acetate (20 mL twice), and the combined organic extracts were dried over anhydrous sodium sulfate and were concentrated *in vacuo*. The crude residue was purified by silica gel

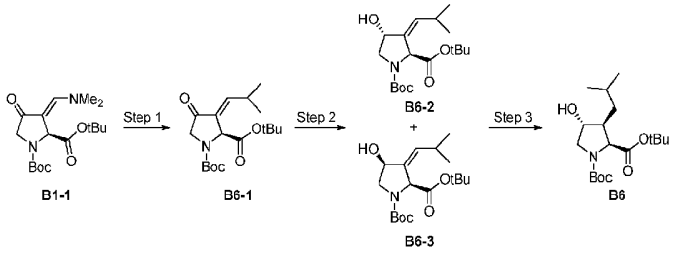
chromatography (0-100% ethyl acetate/hexanes gradient) to afford intermediate **B5-1** (308.8 mg) as a colorless oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{28}NO_5$: 326.2; found: 326.2.

Step 2. Preparation of **B5-2:** To a solution of enone **B5-1** (308 mg, 0.95 mmol) in methanol (4.7 mL) was added cerium(III) chloride heptahydrate (566 mg, 1.52 mmol) at rt under an argon atmosphere. The resulting mixture was cooled to -78 °C, and sodium borohydride (57.7 mg, 1.52 mmol) was added as a solid. After 1 h, the reaction mixture was warmed to 0 °C and saturated aqueous ammonium chloride (20 mL) was added. The resulting mixture was extracted with ethyl acetate (20 mL twice), and the combined organic extracts were dried over anhydrous sodium sulfate and were concentrated *in vacuo* to afford allylic alcohol **B5-2** (319.3 mg) as a colorless oil, which was used directly in the next step without purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{29}NO_5$: 328.2; found: 328.2.

Step 3. Preparation of Intermediate **B5:** To a solution of alcohol **B5-2** (319 mg, 0.98 mmol) in ethanol (4.9 mL) was added Pd/C (10%, 103.9 mg, 0.097 mmol) at rt under an argon atmosphere. The atmosphere was replaced with hydrogen and the reaction mixture was stirred vigorously at rt. After 16 h, the reaction mixture was diluted with ethyl acetate (25 mL) and was filtered through a pad of Celite with ethyl acetate washings (10 mL three times). The filtrate was concentrated *in vacuo* to afford Intermediate **B5** (188 mg), which was used directly in the next step without purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{32}NO_5$: 330.2; found: 330.3.

Preparation of Intermediate B6.

[0133]

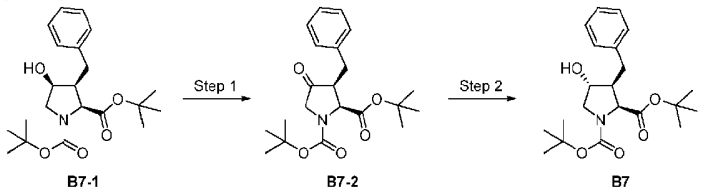


Step 1. Preparation of **B6-1:** A solution of isopropylmagnesium bromide (2.9 M in MeTHF, 3.2 mL, 9.3 mmol) was added dropwise to a cooled solution of **B1-1** (1.02 g, 3.00 mmol) in 60 mL of ether at -78 °C under argon. Reaction mixture was warmed to room temperature and stirred for 3 hours. Reaction mixture was quenched with sat. aqueous NH_4Cl and extracted three times with ether. Combined organics were washed with sat. aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0-30% ethyl acetate in hexanes) to yield **B6-1** (743 mg) as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 6.60 (dd, J = 10.8, 2.4 Hz, 1 H), 5.14 and 5.06 (rotamers, d, J = 2.4 Hz, 1 H), 3.96 (m, 2H), 2.91 (m, 1 H), 1.46 (s, 9H), 1.27 (s, 9H), 1.04 (d, J = 8.8 Hz, 6H). Step 2. Preparation of **B6-2** and **B6-3:** $CeCl_3 \cdot 7H_2O$ (1.32 g, 3.50 mmol) was added to a solution of **B6-1** (740 mg, 2.18 mmol) in 47 mL of methanol at room temperature under argon. After cooling to -78 °C, sodium borohydride (127 mg, 3.34 mmol) was added slowly portionwise. After two hours, reaction mixture was warmed to 0 °C. After fifteen minutes, reaction mixture was quenched with sat. aqueous NH_4Cl and extracted three times with ethyl acetate. Combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a ~3:1 mixture of **B6-2** (major) and **B6-3** (minor) as a colorless film (738 mg), which was used in the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 5.68-5.48 (m, 1H), 4.90-4.31 (m, 2H), 4.05-3.15 (m, 2H), 2.90-2.61 (m, 1 H), 1.50-1.39 (br s, 18H), 1.02 (d, J = 9.2 Hz, 6H).

Step 3. Preparation of Intermediate **B6:** The ~3:1 mixture of **B6-2** and **B6-3** (341 mg, 1.00 mmol) was dissolved in 28 mL of ethyl acetate. Palladium on carbon (10 wt %, 109 mg, 0.11 mmol) was then added and mixture was hydrogenated under an atmosphere of hydrogen for nineteen hours. Mixture was then filtered over Celite, washing with ethyl acetate, and filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0-50% ethyl acetate in hexanes) to yield Intermediate **B6** (141 mg) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.31-4.17 (m, 2H), 3.97-3.85 (m, 1 H), 3.21-3.07 (m, 1 H), 2.35-2.18 (m, 1 H), 1.92-1.78 (m, 1 H), 1.47-1.37 (m, 18H), 1.35-1.19 (m, 2H), 0.94 (d, J = 8.8 Hz, 6H).

Preparation of Intermediate B7.

[0134]

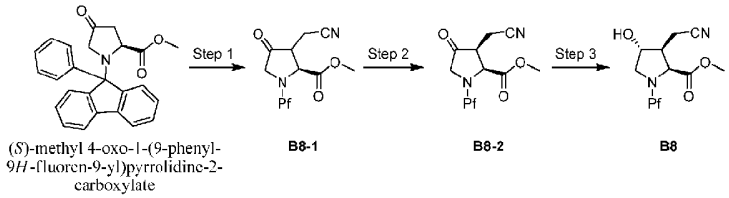


Step 1. Preparation of **B7-2:** To a solution of alcohol **B7-1** (500 mg, 1.33 mmol; prepared according to Barreling, P., et al. Tetrahedron 1995, 51, 4195) in DCM (6.65 mL) was added Dess-Martin periodinane (564 mg, 1.33 mmol) at rt under an argon atmosphere. After 2 h, the reaction mixture was purified directly by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford ketone **B7-2** (431 mg) as a colorless oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{30}NO_5$: 376.2; found: 376.2.

Step 2. Preparation of Intermediate **B7:** To a solution of intermediate **B7-2** (410 mg, 1.09 mmol) and (*R*)-(+)-2-methyl-CBS-oxazaborolidine (Aldrich, 1 M in toluene, 1.09 mL, 1.09 mmol) in THF (5.45 mL) was added BH_3-THF (1 M in toluene, 2.18 mL, 2.18 mmol) at -78 °C under an argon atmosphere. After 1 h, the reaction mixture was quenched with saturated aqueous ammonium chloride solution (15 mL) and the resulting mixture was allowed to warm to rt. The phases where separated and the aqueous phase was extracted twice (20 mL) with DCM. The combined organic layers were dried over anhydrous sodium sulfate, and were concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford Intermediate **B7** (390.9 mg, 4:1 diastereomeric mixture) as a colorless oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{32}NO_5$: 378.2; found: 378.5.

Preparation of Intermediate B8.

[0135]



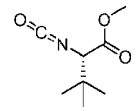
Step 1. Preparation of **B8-1.** n-BuLi (0.44 mL, 1.1 mmol, 2.5 M in hexane) was added to a cold (-78 °C) solution of (S)-methyl 4-oxo-1-(9-phenyl-9H-fluoren-9-yl)pyrrolidine-2-carboxylate (383 mg, 1 mmol, prepared as described in Sardina, F.J., Blanco, M.-J. J. Org. Chem. 1996, 61, 4748) in THF/HMPA (3.8 mL/ 0.4 mL). The resulting solution was stirred at -78 °C to -50 °C for 1.5 h, and then bromoacetonitrile (0.2 mL, 3 mmol) was added. The reaction mixture was stirred while the temperature was allowed to reach -10 °C (4 h). To the reaction mixture was charged with saturated aqueous NH_4Cl (1 mL) and EtOAc (15 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL). Both organic layers were combined, washed with H_2O and brine, and dried over Na_2SO_4. The organic layer was concentrated and purified via silica gel chromatography to afford diastereomeric mixture **B8-1** (170 mg) as colorless oil. Step 2. Preparation of **B8-2.** KHMDS (0.4 mL, 0.4 mmol, 1 M in THF) was added to a cold (-78 °C) solution of **B8-1** (140 mg, 0.33 mmol) in THF/DMPU (1.5 mL/0.75 mL). The resulting solution was stirred at -78 °C for 1.5 h. Then HOAc (0.1 mL) was added. To the reaction mixture was charged with saturated aqueous NH_4Cl (1 mL) and EtOAc (15 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL). Both organic layers were combined, washed with H_2O and brine, and dried over Na_2SO_4. The organic layer was concentrated and purified via silica gel chromatography to afford ketone **B8-2** (120 mg) as colorless oil.

Step 3. Preparation of Intermediate **B8.** To an oven-dried, nitrogen-flushed flask was added BH_3•THF (0.28 mL, 0.28 mmol,) followed by (*R*)-(+)-2-methyl-CBS-oxazaborolidine (0.012 mL, 0.03 mmol, 1.0 M in toluene). A solution of **B8-2** (120 mg, 0.28 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred at rt for 60 min, and then quenched by addition of 1.0 M aqueous HCl (0.2 mL). EtOAc (20 mL) was added and organic phase washed with sat. aqueous $NaHCO_3$ and brine, and

dried over Na_2SO_4. The organic layer was concentrated and purified via silica gel chromatography to afford Intermediate **B8** (100 mg) as colorless oil. LCMS-ESI$^+$ (*m/z*): $[M]^+$ calcd for $C_{27}H_{24}N_2O_3$: 424.49; found: 424.77.

Preparation of Intermediate C1.

[0136]



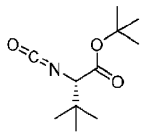
methyl 3-methyl-N-(oxomethylene)-L-valinate

C1

[0137] Methyl 3-methyl-N-(oxomethylene)-L-valinate (Intermediate **C1**) was prepared according to Step 3 of Intermediate B1 of International Patent Publication No. WO 2010/11566 (hereinafter "WO'566"), p 14.

Preparation of Intermediate C2.

[0138]



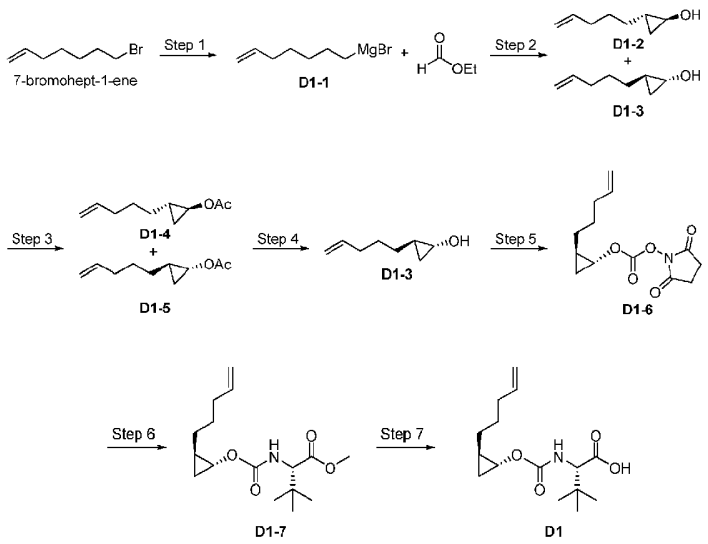
tert-butyl 3-methyl-N-(oxomethylene)-L-valinate

C2

[0139] Intermediate **C2** (tert-butyl 3-methyl-N-(oxomethylene)-L-valinate) was prepared in a similar fashion to Intermediate **C1,** substituting tert-butyl 3-methyl-L-valinate (Bachem AG) for methyl 3-methyl-L-valinate in Step 3 of intermediate B1 of WO'566, p14.

Preparation of Intermediate D1.

[0140]



Steps 1 and 2. Preparation of *trans*-cyclopropanol mixture **D1-2** and **D1-3:** THF (1000 mL) was introduced in a three neck round bottomed flask containing Mg (32.2 g, 1.34 mol). A solution of 7-bromohept-1-ene (216 g, 1.22 mol) in THF (600 mL) was introduced to an addition funnel. One crystal of iodine and 20 mL of 7-bromohept-1-ene solution were added to the reaction. The solution was heated to reflux, and the remainder of the 7-bromohept-1-ene solution was added drop wise. After the addition was complete, the mixture was refluxed for an additional 2 h then allowed to cool to rt to produce a solution of Grignard reagent **D1-1,** which was then added dropwise to a solution of ethyl formate (30 g, 0.41 mol) and Ti(O*i*-Pr)$_4$ (115.2 g, 0.41 mol) in THF (1200 mL) at rt. After stirring overnight, the mixture was poured into 1600 mL of 10% aqueous H_2SO_4 and extracted with MTBE (1500 mL three times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford 31.0 g of a mixture of *trans*-cyclopropyl alcohols **D1-2** and **D1-3** as a yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 5.77-5.70 (m, 1 H), 4.96-4.86 (m, 2H), 3.15-3.12 (m, 1 H), 2.03-1.98 (m, 2H), 1.75 (br s, 1 H), 1.45-1.37 (m, 2H), 1.20-1.15 (m, 1 H), 1.06-1.01 (m, 1 H), 0.89-0.82 (m, 1 H), 0.63-0.59 (m, 1 H), 0.24 (q, *J* = 6.0 Hz, 1 H).
Step 3. Preparation of cyclopropyl acetate mixture **D1-4** and **D1-5:** To a 1000 mL round bottom flask was added *trans*-cyclopropyl alcohol mixture **D1-2** and **D1-3** (60.3 g, 0.48 mol), 700 mL of DCM and TEA (62.9 g, 0.62 mol) prior to cooling the solution in an acetone/ice bath to an internal temp of < 5 °C. Acetyl chloride (41.3 g, 0.53 mol) was added dropwise to the solution over a 30 min period while maintaining an internal temp < 10 °C. The resulting slurry was then warmed to rt and stirred for 2 h. The reaction mixture was diluted with 350 mL of water. The biphasic mixture was transferred to a separatory funnel and the aqueous layer removed. The organic layer was washed with 480 mL of 2 N aqueous HCl and then with 500 mL of sat. aqueous $NaHCO_3$ prior to drying over $MgSO_4$. The solvent was removed *in vacuo*. The residue was purified by silica gel chromatography to afford a mixture **D1-4** and **D1-5** (56.3 g) as a yellow oil. TLC Information (PE/EtOAc =5/1) R_f (starting material) = 0.4; R_f (product) = 0.8.

Step 4. Preparation of **D1-3:** To a 1000 mL round-bottom flask was added a solution of mixture **D1-4** and **D1-5** (39 g, 0.23 mol) in 680 mL of MTBE saturated with aqueous 0.1 M pH 7 phosphate buffer. The flask was placed in an ice bath to maintain an internal temperature of approximately 10 °C throughout the hydrolysis reaction which was initiated by the addition of 3.0 g of Novozyme 435. The reaction was aged at 10 °C for approximately 6 h until conversion had reached about 40%. The reaction mixture was filtered, and the solid immobilized enzyme was washed three times with 200 mL of MTBE. The resulting MTBE solution was concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford **D1-3** (11.3 g) as a yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.80-5.75 (m, 1 H), 5.02-4.91 (m, 2H), 3.20-3.17 (m, 1 H), 2.09-2.03 (m, 3H), 1.50-1.43 (m, 2H), 1.26-1.22 (m, 1 H), 1.17-1.08 (m, 1 H), 1.07-0.89 (m, 1 H), 0.70-0.65 (m, 1 H), 0.32-0.27 (m, 1 H).

Step 5. Preparation of **D1-6:** Cyclopropanol **D1-3** (17.7 g, 0.140 mol) was dissolved in 300 mL of MeCN at 0 °C. To the solution was added DSC (72.0 g, 0.280 mol) and TEA (42.42 g, 0.420 mol). The reaction mixture was warmed to 40 °C and stirred overnight and then concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford **D1-6** (25.8 g) as a yellow solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.84-5.77 (m, 1 H), 5.05-4.96 (m, 2H), 4.09-4.03 (d, *J* = 24 Hz, 1 H), 2.86 (s, 4H), 2.12-2.06 (m, 2H), 1.58-1.51 (m, 2H), 1.33-1.27 (m, 3H), 1.09 (m, 1 H), 0.68-0.62 (m, 1 H).

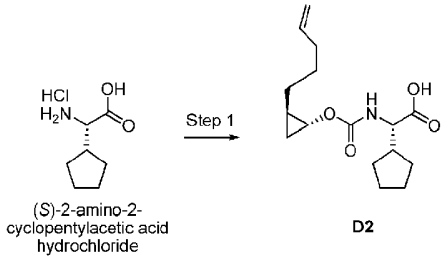
Step 6. Preparation of **D1-7:** To a solution of **D1-6** (10 g, 0.0374 mol) in THF (374 mL) was added L-tert-leucine methyl ester hydrochloride (10.2 g , 0.056 mol) and TEA (11.3 g, 0.112 mol). The solution was stirred overnight at 40 °C. The mixture was concentrated *in vacuo*. The residue was diluted with EtOAc and washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford **D1-7** (10.2 g) as a

yellow oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{28}NO_4$: 298.2; found: 298.0.

Step 7. Preparation of Intermediate **D1:** A solution of **D1-7** (20 g, 0.067 mol) in 2:1 mixture of MeOH/H_2O (447 mL/223 mL) was treated with LiOH•H_2O (11.3 g, 0.269 mol) and then heated at 60 °C for 4 h. The reaction mixture was cooled, concentrated to half volume and extracted with MTBE. Then the aqueous solution was acidified with aqueous 1 N HCl (400 mL) and extracted with EtOAc (400 mL × 3), the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford Intermediate **D1** (18 g). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 10.5-9.4 (br, 1 H), 5.82-5.71 (m, 1 H), 5.20-5.17 (m, 1 H), 4.99-4.91 (m, 2H), 4.19-4.16 (m, 1 H), 3.86-3.68 (m, 1 H), 2.09-2.03 (m, 2H), 1.53-1.32 (m, 2H), 1.30-1.20 (m, 2H), 1.18-1.13 (m, 1 H), 1.11-0.99 (s, 9H), 0.80-0.75 (m, 1 H), 0.49-0.47 (m, 1 H).

Preparation of Intermediate D2.

[0141]



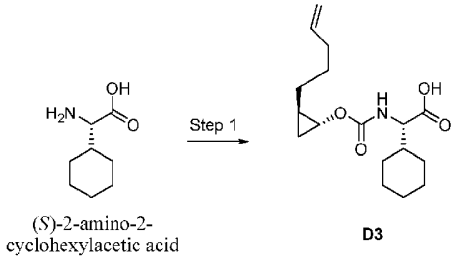
(*S*)-2-amino-2-cyclopentylacetic acid hydrochloride

D2

[0142] Step 1. Preparation of Intermediate **D2:** To a suspension of **D1-6** (600 mg, 2.25 mmol) and (S)-2-amino-2-cyclopentylacetic acid hydrochloride salt (386 mg, 2.7 mmol, Betapharma Inc.) in THF (20 mL) were added distilled water (6 mL) and triethylamine (0.94 mL, 6.74 mmol). The homogeneous solution was allowed to stir for ~ 18 h. The THF was evaporated and the aqueous residue was diluted with water (20 mL). The mixture was basified with 1 N NaOH (pH > 10) and then washed twice (20 mL) with ethyl acetate. The aqueous phase was then acidified with 1 N HCl (pH < 2) and the resulting solution was extracted twice (20 mL) with ethyl acetate. The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated to afford Intermediate **D2** (500 mg) as a brown oil. This was used without purification in a subsequent step. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{16}H_{26}NO_4$: 296.2; found: 296.3.

Preparation of Intermediate D3.

[0143]



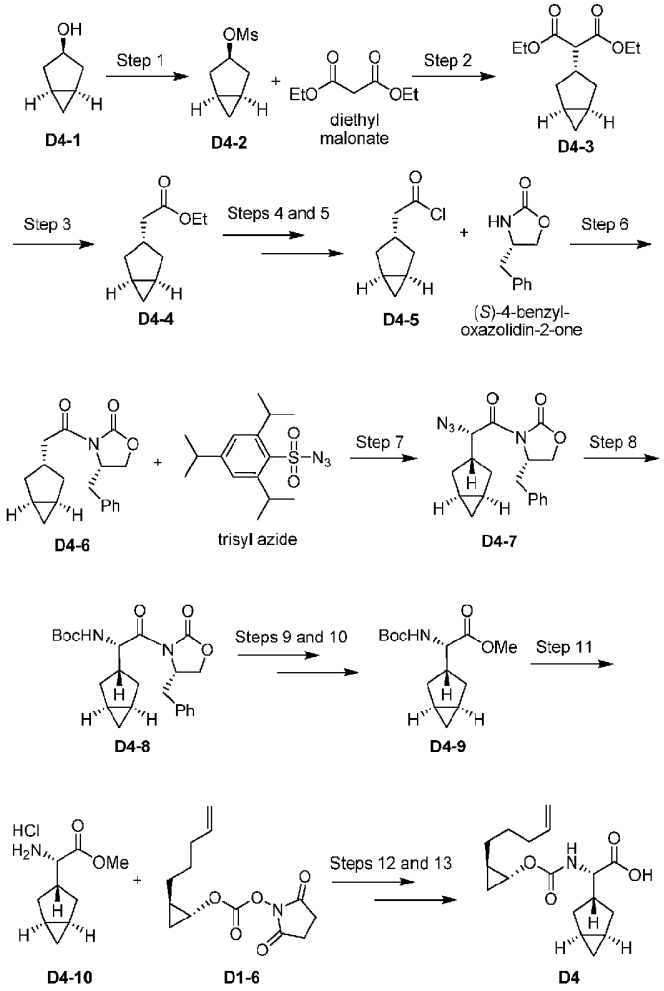
(*S*)-2-amino-2-cyclohexylacetic acid

D3

[0144] Step 1. Preparation of Intermediate **D3:** To a suspension of **D1-6** (800 mg, 3 mmol) and (S)-2-amino-2-cyclohexylacetic acid (519 mg, 3.3 mmol; Alfa Aesar) in water (15 mL) was added K_3PO_4 (1.27 g, 6 mmol). The homogeneous solution was allowed to stir at rt for 5 h. To the reaction mixture was charged with water (15 mL) and EtOAc (15 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL). Organic layers were combined, washed with 1 N HCl, H_2O and brine, and dried over Na_2SO_4. Concentration of the organic solution afforded Intermediate **D3** (850 mg) as an oil that was used subsequently without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{28}NO_4$: 310.4; found: 310.3.

Preparation of Intermediate D4.

[0145]



Step 1. Preparation of **D4-2:** Bicyclic alcohol **D4-1** (2.9 g, 29.5 mmol, prepared according to Section A, Intermediate 1 of U.S. Patent No. 8,178,491 B2 (hereinafter "US '491"), p 192.) was dissolved in DCM (60 mL) and TEA (8.2 mL, 59 mmol) was added. The stirred solution was cooled to 0 °C and MsCl (3.4 mL, 44 mmol) was added. The reaction mixture was allowed to warm to rt gradually. After 18 h, the reaction mixture was poured into H_2O. The aqueous layer was extracted 2 x with DCM then the combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (20% to 50% EtOAc/Hex) to afford **D4-2** (3.73 g).

Step 2. Preparation of **D4-3:** NaH (1.69 g, 42.3 mmol) was suspended in 100 mL THF and the mixture was cooled to 0 °C. Diethyl malonate (6.4 mL, 47 mmol) was added dropwise over 4 min and the stirred mixture was warmed to rt. After another hour, mesylate **D4-2** (3.73 g, 21.2 mmol) in 20 mL THF was added and the reaction mixture was heated to reflux for 15 h. After this period, the reaction mixture was cooled to rt and poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted 2 x with EtOAc. Then, the organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (0% to 15% EtOAc/Hex) to afford **D4-3** (4.64 g).

Step 3. Preparation of **D4-4:** Malonate **D4-3** (4.64 g, 19.3 mmol) was dissolved in 20 mL DMSO then NaCl (1.24 g, 21.2 mmol) and water (0.694 mL, 38.6 mmol) were added. The stirred mixture was heated to 170 °C for 48 h then cooled to rt and diluted with Et_20. The organic solution was washed with H_2O twice, then brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (5% to 15% EtOAc/Hex) to afford **D4-4** (2.83 g).

Steps 4 and 5. Preparation of **D4-5:** A solution of ethyl ester **D4-4** (2.83 g, 16.8 mmol) and LiOH (1 M in H_2O, 34 mL, 34 mmol) in EtOH (68 mL) was stirred at rt o/n then concentrated under reduced pressure to remove EtOH. The remaining material was

diluted with H_2O and washed twice with DCM. The aqueous phase was acidified to pH 1-2 with 10% HCl and then extracted three times with DCM. This DCM solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude carboxylic acid was dissolved in DCM (100 mL) and treated with DMF (5 drops). Oxalyl chloride (2.2 mL, 25 mmol) was added carefully. After stirring o/n, the reaction mixture was concentrated under reduced pressure to afford **D4-5,** which was carried on without further purification.

Step 6. Preparation of **D4-6:** (S)-4-Benzyl-2-oxazolidinone (3.57 g, 20.2 mmol) was dissolved in THF (80 mL) and cooled to -78 °C. *n*-BuLi (1.6 M in hexane, 12.6 mL, 20.2 mmol) was added dropwise over 7 min and the reaction mixture was allowed to stir at -78 °C for 30 min. This solution, containing the lithiated oxazolidinone was then added by cannula to a -78 °C solution of acid chloride **D4-5** (16.8 mmol) in THF (80 mL) over 6 min. After stirring at -78 °C for an additional 30 min, the reaction mixture was quenched by addition of 1 M aqueous $NaHSO_4$. The aqueous phase was extracted with EtOAc and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (10% to 40% EtOAc/Hex) to afford **D4-6** (4.32 g). LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{18}H_{22}NO_3$: 300.16; found: 300.14.

Step 7. Preparation of **D4-7:** A solution of KHMDS (0.5 M in PhMe, 3.4 mL, 1.7 mmol) in THF (5 mL) was cooled to -78 °C and a separate -78 °C solution of oxazolidinone **D4-6** (465 mg, 1.55 mmol) in THF (5 mL) was added dropwise by cannula. After 30 min, a -78 °C solution of trisyl azide (576 mg, 1.86 mmol) in THF (5 mL) was added by cannula. Three min later, the reaction was quenched by addition of AcOH (0.41 mL, 7.13 mmol) and the reaction mixture was heated to 30 °C for 2 h. After cooling, the mixture was poured into brine. The aqueous layer was extracted three times with DCM. The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (4% to 25% EtOAc/Hex) to afford azide **D4-7** (367 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_4O_3$: 341.16; found: 341.10.

Step 8. Preparation of **D4-8:** Azide **D4-7** (367 mg, 1.08 mmol) and di-*tert*-butyl dicarbonate (471 mg, 2.16 mmol) were dissolved in EtOAc (20 mL). 10% Pd/C (197 mg) was added and the atmosphere replaced with H_2. The suspension was stirred under 1 atm H_2 for 20 h, then filtered over Celite and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (15% to 30% EtOAc/Hex) to afford **D4-8** (376 mg). LCMS-ESI$^+$ (*m/z*): $[M-(t\text{-Bu})+H]^+$ calcd for $C_{19}H_{23}N_2O_5$: 359.16; found: 359.43.

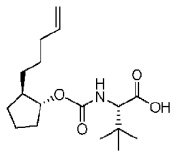
Steps 9 and 10. Preparation of **D4-9:** Carbamate **D4-8** (376 mg, 0.907 mmol) was dissolved in THF (9 mL) and cooled to 0 °C. H_2O_2 (30% in H_2O, 0.463 mL, 4.54 mmol) and LiOH (1 M in H_2O, 2.7 mL, 2.7 mmol) were added. The reaction was allowed to stir at 0 °C for another 2 h and was then concentrated under reduced pressure. The resulting concentrate was poured into H_2O and the aqueous solution was washed twice with Et_2O, then acidified to pH 1-2 and extracted three times with DCM. The combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was dissolved in DCM (8 mL) and MeOH (1 mL) and treated with trimethylsilyldiazomethane (2 M in hexane, 0.9 mL, 1.8 mmol). After stirring for 40 min at rt, the reaction was quenched by addition of 10% AcOH/MeOH and concentrated under reduced pressure. The residue was purified by silica gel chromatography (4% to 25% EtOAc/Hex) to afford **D4-9** (167 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (d, *J* = 7.8 Hz, 1 H), 4.22 (t, *J* = 7.0 Hz, 1 H), 3.70 (s, 3H), 1.89 (m, 1 H), 1.77-1.46 (m, 4H), 1.42 (s, 9H), 1.22 (m, 2H), 0.28 (dd, J = 7.2 Hz, 13.3 Hz, 1 H), 0.13 (d, *J* = 3.7 Hz, 1 H).

Step 11. Preparation of **D4-10:** Carbamate **D4-9** (223 mg, 0.828 mmol) was dissolved in DCM (4 mL) and treated with HCl (4.0 M in dioxane, 1 mL, 4.0 mmol). After stirring at rt for 17 h, the reaction mixture was concentrated under reduced pressure to afford amine hydrochloride salt **D4-10,** which was carried on without purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_9H_{16}NO_2$: 170.12; found: 170.04.

Steps 12 and 13. Preparation of Intermediate **D4:** Amine hydrochloride salt **D4-10** (0.828 mmol, theoretical) in H_2O (1.4 mL) was treated with a freshly prepared solution of **D1-6** (1.35 mmol) in DMF (1.4 mL). K_3PO_4 (703 mg, 3.31 mmol) was added and the reaction mixture was stirred for 2 h at rt. After dilution with EtOAc, the organic layer was washed with 10% aqueous HCl and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0% to 25% EtOAc/Hex) to afford the expected carbamate (239 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{28}NO_4$: 322.20; found: 323.00. This material (239 mg, 0.744 mmol) was dissolved in MeOH and treated with LiOH (1.0 M in H_2O, 5.0 mL, 5.0 mmol). After stirring at rt for 1 h, the MeOH was removed under reduced pressure. The aqueous solution was acidified to pH 1-2 with 10% aqueous HCl and was extracted three times with DCM. The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford Intermediate **D4** (229 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{26}NO_4$: 308.2; found: 307.9.

Preparation of Intermediate D5.

[0146]

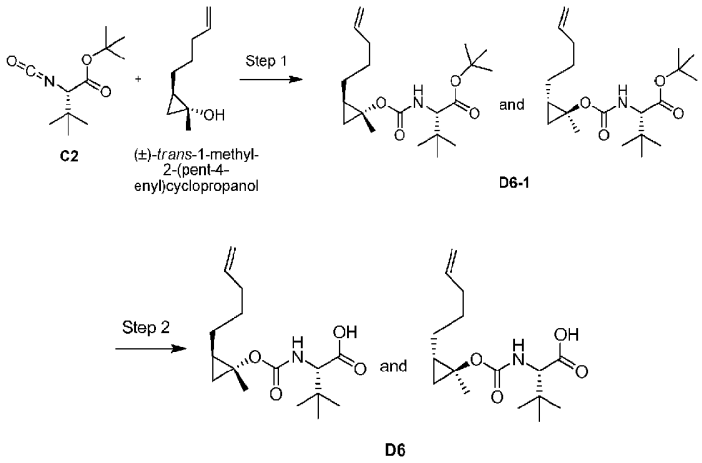


D5

[0147] Intermediate **D5** was prepared according to the procedure detailed in Li, H., et al. Synlett 2011, 10, 1454.

Preparation of Intermediate mixture D6.

[0148]



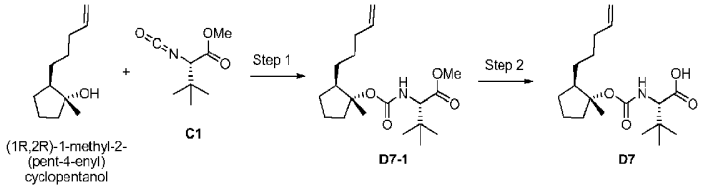
C2 (±)-*trans*-1-methyl-2-(pent-4-enyl)cyclopropanol D6-1 D6

Step 1. Preparation of diastereomeric carbamate mixture **D6-1:** Intermediate **C2** (1.34 g, 6.31 mmol), (±)-trans-1-methyl-2-(pent-4-enyl)cyclopropanol (590 mg, 4.208 mmol; prepared according to procedure for Intermediate C3, WO2011014487, p. 36), DMAP (514 mg, 4.21 mmol), and DIPEA (2.93 mL, 16.83 mmol) were combined in toluene (14 mL). The reaction was heated at 90 °C for 18 h. The reaction was diluted with Et_2O (25 mL) and 1 N aqueous HCl (75 mL), stirred well, and organics were removed. The aqueous layer was extracted three times with ether (50 mL), the organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a crude oil, which was purified via silica gel chromatography to give 1:1 diastereomeric mixture **D6-1** as a clear oil (820 mg). LCMS-ESI$^+$ (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{35}NNaO_4$: 376.3; found: 376.2.

Step 2: Preparation of diastereomeric Intermediate mixture **D6.** The diastereomeric mixture **D6-1** was taken up in DCM (2 mL) and treated with TFA (2 mL) at room temperature. After 1.5 h, the reaction was concentrated *in vacuo* and co-evaporated with chloroform repeatedly to remove residual TFA and purified via silica gel chromatography to give 1:1 diastereomeric mixture of Intermediate **D6** as a brown oil, (536 mg). LCMS-ESI$^+$ (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{27}NNaO_4$: 320.2; found: 320.1.

Preparation of Intermediate D7.

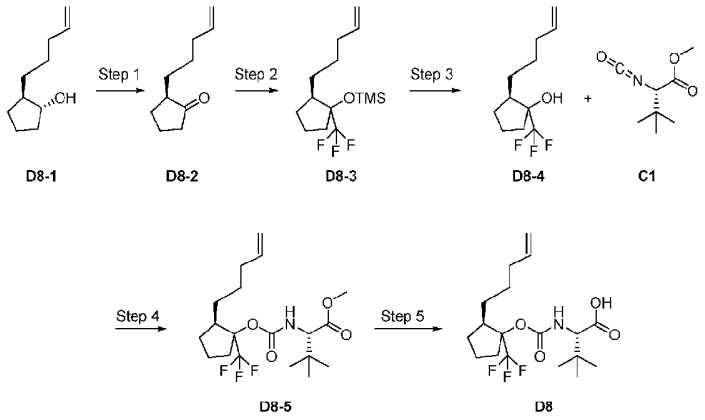
[0149]



[0150] Step 1. Preparation of **D7-1:** (1 R,2R)-1-methyl-2-(pent-4-enyl)cyclopentanol (220.9 mg, 1.313 mmol; prepared according to procedure for Intermediate B26, International Patent Publication No. WO 2008/057209 (hereinafter "WO '209"), p. 45) and Intermediate **C1** (337.1 mg, 1.969 mmol) were treated with DIPEA (0.91 mL, 5.252 mmol) and DMAP (160.4 mg, 1.313 mmol) in toluene (4.4 mL). The mixture was heated at 85 °C for 21 h. The solution was diluted with ether (80 mL). The solution was washed with 1 N aqueous HCl (30 mL) and brine (30 mL) successively. Obtained organic layer was dried over Na_2SO_4. After removal of drying agent by a filtration, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (13% ethyl acetate in hexanes) to give **D7-1** (249.5 mg, 0.735 mmol) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers expressed as total H value x fraction present) δ 5.76-5.92 (m, 1 H), 5.12 (d, *J* = 9.6 Hz, 1 H), 5.02 (d, *J* = 16.8 Hz, 1 H), 4.96 (d, *J* = 9.6 Hz, 1 H), 4.13 (d, *J* = 9.6 Hz, 1 H), 3.81 (s, 3 x 4/10H), 3.73 (s, 3 x 6/10H), 1.80-2.15 (m, 7H), 1.04-1.74 (m, 6H), 1.36 (s, 3H), 1.04 (s, 9 x 4/10H), 0.97 (s, 9 x 6/10H). Step 2. Preparation of Intermediate **D7:** Ester **D7-1** (249.5 mg, 0.735 mmol) was treated with 2 M aqueous LiOH aqueous solution (2 mL, 4.0 mmol) in MeOH/THF (4 mL / 4 mL) at rt for 25 h. The reaction mixture was then treated with 1 N aqueous HCl (5 mL) and aqueous brine (25 mL) to slightly acidify. The mixture was extracted three times with CH_2Cl_2 (30 mL). The organic layer was washed with aqueous brine (30 mL). Obtained organic layer was dried over Na_2SO_4. After removal of drying agent by filtration, the solvent was removed under a reduced pressure to give Intermediate **D7** (191.2 mg, 0.587 mmol) as a colorless oil which was used subsequently without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (br s, 1 H), 5.72-5.90 (m, 1 H), 5.12 (d, *J* = 9.6 Hz, 1 H), 5.00 (d, *J* = 16.8 Hz, 1 H), 4.94 (d, *J* = 9.6 Hz, 1 H), 4.13 (d, *J* = 9.6 Hz, 1 H), 1.80-2.16 (m, 7H), 1.04-1.74 (m, 6H), 1.35 (s, 3H), 1.02 (s, 9H).

Preparation of Intermediate mixture D8.

[0151]



Step 1. Preparation of **D8-2:** To a solution of intermediate **D8-1** (500 mg, 3.24 mmol, prepared according to WO '209, p. 36) in DCM (6.65 mL) was added Dess-Martin periodinane (1.37 g, 3.24 mmol) at rt under an argon atmosphere. After 6 h, the reaction mixture was filtered through a pad of Celite and was directly purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford ketone **D8-2** (252 mg) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1 H), 5.05 - 4.92 (m, 2H), 2.38 - 1.93 (m, 7H), 1.87 - 1.68 (m, 2H), 1.60 - 1.37 (m, 3H), 1.35 - 1.20 (m, 1 H).

Step 2. Preparation of diastereomeric mixture **D8-3:** To a solution of ketone **D8-2** (385 mg, 2.53 mmol) and $TMSCF_3$ (749 µL, 5.07 mmol) in THF (2.3 mL) was added CsF (7.0 mg, 46 µmol) at rt under an argon atmosphere. After 2.5 h, the reaction mixture was diluted with water (10 mL) and the resulting mixture was extracted twice with DCM (10 mL). The combined organic layers were dried over anhydrous sodium sulfate, and were concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford silyl ether **D8-3** (714 mg, 1:1 diastereomeric mixture) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (ddt, *J* = 13.3, 10.1, 6.7 Hz, 1 H), 4.91 - 4.76 (m, 2H), 2.02 - 1.00 (m, 13H), 0.00 (s,

9H).

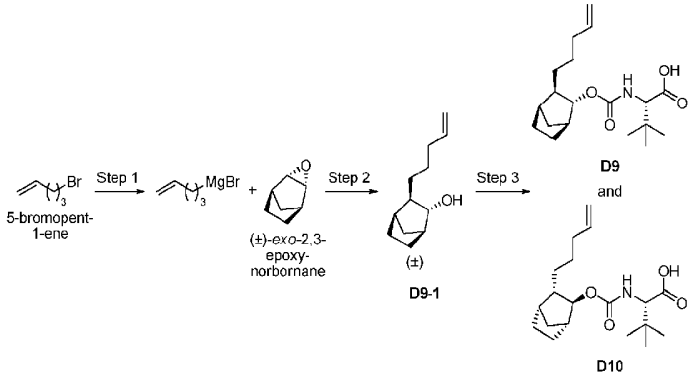
Step 3. Preparation of diastereomeric mixture **D8-4:** To a solution of **D8-3** (700 mg, 2.38 mmol) in THF (11.9 mL) was added TBAF (1 M in THF, 2.38 mL, 2.38 mmol) at rt under an argon atmosphere. After 30 min, the reaction mixture was diluted with dichloromethane (100 mL). The resulting mixture was washed with saturated aqueous sodium bicarbonate solution (75 mL), was dried over anhydrous sodium sulfate, and was concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford alcohol **D8-4** (418 mg, 1:1 diastereomeric mixture) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (dt, *J* = 16.8, 6.6 Hz, 1 H), 5.09 - 4.88 (m, 2H), 2.20 - 1.91 (m, 4H), 1.86 - 1.08 (m, 10H).

Step 4. Preparation of diastereomeric mixture **D8-5:** A solution of **D8-4** (380 mg, 1.72 mmol), Intermediate **C1** (295.7 mg, 1.72 mmol), DIPEA (1.20 mL, 6.88 mmol), and DMAP (210 mg, 1.72 mmol) in toluene (8.6 mL) was heated to 85 °C under an argon atmosphere. After 20 h, the reaction mixture was allowed to cool to rt and was diluted with ethyl acetate (100 mL). The resulting mixture was washed with 1 N HCl solution (50 mL), saturated aqueous sodium bicarbonate solution (50 mL), and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate, and was concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford carbamate **D8-5** (550 mg, 1:1 diastereomeric mixture) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.7, 9.8, 6.6 Hz, 1 H), 5.37 (d, *J* = 9.4 Hz, 1 H), 5.06 - 4.89 (m, 2H), 4.16 - 4.07 (m, 1 H), 3.75 (s, 3H), 2.84 - 2.29 (m, 2H), 2.27 - 1.89 (m, 3H), 1.85 - 1.12 (m, 8H), 0.98 (s, 9H).

Step 5. Preparation of diastereomeric Intermediate mixture **D8:** To a solution of carbamate **D8-5** (500 mg, 1.27 mmol) in DCE (6.4 mL) was added trimethyltin hydroxide (2.30 g, 12.7 mmol) at rt under an argon atmosphere, and the resulting mixture was heated to 65 °C. After 21 h, the reaction mixture allowed to cool to rt and was diluted with 1 N HCl solution (50 mL). The resulting mixture was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated *in vacuo* to afford Intermediate **D8** (575 mg, 1:1 diastereomeric mixture) as a colorless oil, which was used subsequently without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 - 5.71 (m, 1 H), 5.32 (d, *J* = 9.3 Hz, 1 H), 5.07 - 4.89 (m, 2H), 4.16 (d, *J* = 9.8 Hz, 1 H), 2.83 - 2.30 (m, 2H), 2.27 - 1.87 (m, 3H), 1.83 - 1.12 (m, 8H), 1.04 (s, 9H).

Preparation of Intermediate mixture D9 and D10.

[0152]

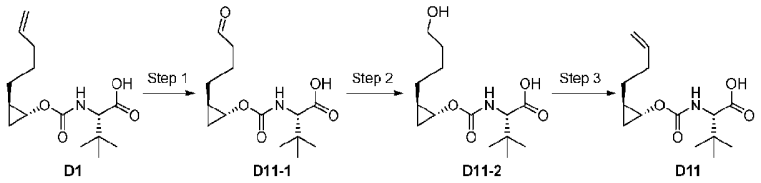


[0153] Steps 1 and 2: Preparation of racemate **D9-1:** Magnesium metal (1.32 g, 54.3 mmol) was added to a 2-neck flask fitted with a reflux condenser and the vessel was flushed with Ar. THF (42 mL) was added followed by iodine (ca. 5 mg). The stirred suspension was heated to 45 °C and 5-bromopent-1-ene was added (1.2 g, 8.1 mmol) in one portion. After stirring several minutes, additional 5-bromopent-1-ene (5.5 g, 37 mmol) was added at a rate sufficient to maintain gentle reflux. The resulting mixture was stirred at 50 °C for 15 min and was then cooled to ambient temperature and used immediately in the following step. A suspension of CuI (630 mg, 3.3 mmol) in THF (24 mL) under Argon was cooled to -5 °C. An aliquot of pent-4-enylmagnesium bromide (ca. 0.95 M, 20 mL, 19 mmol) prepared in step 1 was added over 5 min, and the resulting mixture was stirred for an additional 15 min. The reaction mixture was then cooled to -20 °C, and (±)-exo-2,3-epoxynorbornane (1.5 g, 14 mmol) was added as a solution in THF (5 mL) over 1 min. Two additional portions of THF (2.5 mL each) were used to ensure complete transfer, and the resulting mixture was stirred for 20 min. The reaction was then removed from the cold bath and warmed to rt. After stirring an

additional 1.75 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and was filtered with EtOAc (100 mL) and H_2O (100 mL) through Celite. The phases were separated, and the organic phase was dried over Na_2SO_4, filtered, and concentrated to afford (±)-**D9-1** as a colorless residue (813 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 - 5.67 (m, 1 H), 5.04 - 4.86 (m, 2H), 3.12 (s, 1 H), 2.20 - 1.92 (m, 5H), 1.69 - 1.57 (m, 1 H), 1.55 - 1.12 (m, 9H), 1.03 - 0.84 (m, 1 H). Step 3. Preparation of diastereomeric Intermediate mixture **D9** and **D10:** Alcohol mixture (±)-**D9-1** (813 mg, 4.51 mmol) was dissolved in DMF (4.5 mL). Pyridine (370 µL, 4.5 mmol) was added followed by DSC (1.5 g, 5.8 mmol). The reaction mixture was heated to 45 °C and was stirred for 4 h. The reaction mixture was then cooled to 0 °C and water (4.5 mL) was added dropwise over 2 min. The reaction mixture was stirred for 5 min and was removed from the cold bath. After an additional 5 min, the reaction mixture was cooled to 0 °C and L-tert-leucine (835 mg, 6.37 mmol) and K_3PO_4 (2.70 g, 12.7 mmol) were added. The mixture was stirred for 10 min and was removed from the cold bath. After stirring an additional 24 h, the mixture was diluted with EtOAc (30 mL), acidified with 1 M aqueous HCl (15 mL), and diluted with 0.2 M aqueous HCl (15 mL). The phases were separated, and the organic phase was washed with 0.2 M aqueous HCl (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated to afford diastereomeric Intermediate mixture **D9** and **D10** (1.64 g). LCMS-ESI$^-$ (*m/z*): $[M-H]^-$ calcd for $C_{19}H_{30}NO_4$: 336.2; found: 336.0.

Preparation of Intermediate D11.

[0154]



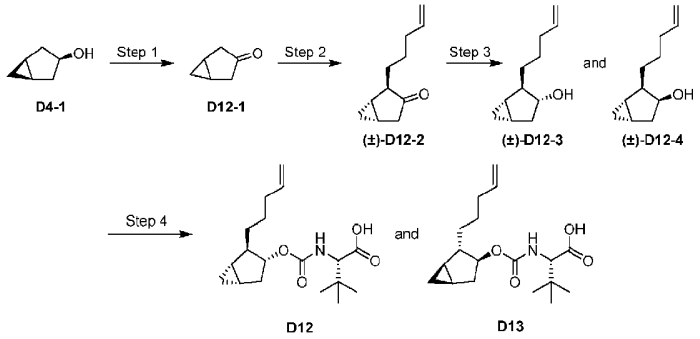
Step 1. Preparation of **D11-1:** To a mixture of **D1** (1.0 g, 3.53 mmol), sodium periodate (2.26 g, 10.59 mmol) in 24 mL THF and 12 mL water was added Os EnCat™ 40 (0.25 mmol/g loading, 282 mg, 0.071 mmol, Sigma-Aldrich). The mixture was stirred for 3 days. Water (50 mL) was added and the mixture was filtered. The filter cake was washed with water (total volume 400 mL) and ethyl acetate (total volume 600 mL). The filtrate layers were separated. The organic phase was dried over sodium sulfate, filtered and concentrated to give **D11-1** (1.56 g) which was used without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{24}NO_5$: 286.2 found: 286.1.

Step 2. Preparation of **D11-2:** To a solution of **D11-1** (3.05 g, 10.7 mmol) in MeOH (50 mL) at 0 °C was added sodium borohydride in portions (809 mg, 21.4 mmol). The reaction mixture was stirred at rt for 6 h. The mixture was diluted with 50 mL ethyl acetate and 50 mL brine and the layers were separated. The organic phase was extracted with two 25 mL portions of ethyl acetate. The combined organic phase was dried over sodium sulfate, filtered and concentrated. The crude product mixture was purified by silica gel chromatography (EtOAc in hexanes: 10% to 100%) to give **D11-2** (380 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{26}NO_5$: 288.2; found: 288.1.

Step 3. Preparation of Intermediate **D11:** To a solution of **D11-2** (283 mg, 0.98 mmol) in THF (2.8 mL) at 0 °C was added 1-nitro-2-selenocyanatobenzene (336 mg, 1.47 mmol) and tributylphosphine (363 µL, 1.47 mmol). The cooling bath was removed and the mixture was stirred for 25 minutes at rt. The reaction was again cooled to 0 °C and was treated with 30% hydrogen peroxide solution (0.665 mL, 5.85 mmol) and stirred for 1 h at rt and then heated at 60 °C for 1 h. The reaction was diluted with EtOAc and the desired product was extracted into aqueous sodium bicarbonate. The bicarbonate extract was acidified with 2 N HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to give Intermediate **D11** (136 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{24}NO_4$: 270.2; found: 270.1.

Preparation of Intermediate mixture D12 and D13.

[0155]



Step 1: Preparation of **D12-1:** To a solution of $K_2O_2O_7$ (121 g, 0.41 mol) in H_2O (1.5 L) was added dropwise H_2SO_4 (143 g, 1.46 mol) at rt and the mixture was stirred for 1 h. The mixture was then cooled to 0 °C and **D4-1** (80 g, 0.814 mol; prepared according to Section A, Intermediate 1 of US '491, p 192.) in MTBE (1.5 L) was added dropwise. The reaction mixture was stirred at rt for 2 h. The aqueous phase was extracted with MTBE (3 x 500 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by distillation (20 mmHg, bp: 60 - 62 °C) to provide **D12-1** as a pale yellow liquid (60 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 - 2.63 (m, 2H), 2.14 - 2.19 (d, *J* = 20 Hz, 2H), 1.52 - 1.57 (m, 2H), 0.89 - 0.94 (m, 1 H), -0.05 - -0.02 (m, 1 H).

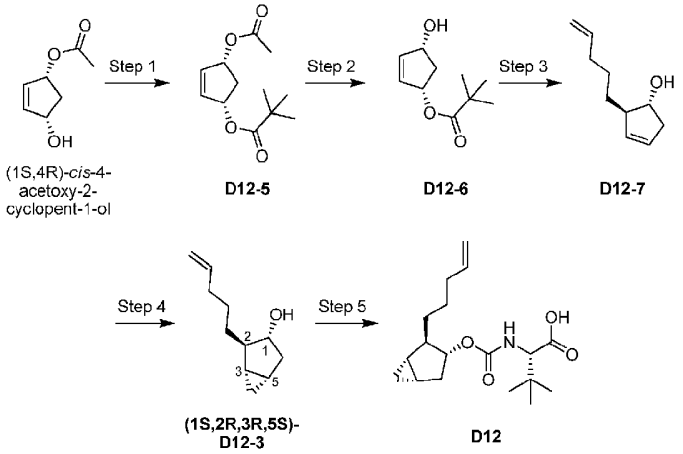
Step 2: Preparation of **(±)-D12-2:** Under Ar, a mixture of THF (4.4 mL) and HMPA (1.8 mL) was cooled to -78 °C. A 1 M solution of LiHMDS in THF (2.2 mL, 2.2 mmol) was added. Ketone **D12-1** (202 mg, 2.10 mmol) was added as a solution in THF (2 mL) over 1 min, washing with additional THF (2 x 1 mL) to ensure complete transfer. After 25 min, 5-iodopent-1-ene (prepared according to Jin, J. et. al. J. Org. Chem. 2007, 72, 5098-5103) (880 mg, 4.5 mmol) was added over 30 s by syringe. After 10 min, the reaction was placed in a cold bath at -45 °C and was warmed to -30 °C over 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl (15 mL) and was diluted with EtOAc (30 mL) and H_2O (15 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to afford a crude residue that was purified by silica gel chromatography (0% to 15% EtOAc in hexanes) to provide (+/-) **-D12-2** a colorless oil (162 mg). ^{1}H NMR (400 MHz, $CDCl_3$) 5.82 - 5.67 (m, 1 H), 5.03 - 4.87 (m, 2H), 2.61 - 2.51 (m, 1H), 2.11 (d, *J* = 19.1 Hz, 1 H), 2.08 - 1.99 (m, 3H), 1.61 - 1.40 (m, 5H), 1.36 - 1.28 (m, 1 H), 0.92 - 0.81 (m, 1 H), -0.03 - -0.11 (m, 1 H).

Step 3: Preparation of **(±)-D12-3** and **(±)-D12-4:** A solution of **(±)-D12-2** (142 mg, 0.865 mmol) in THF (4 mL) was cooled to -78 °C. A 1 M THF solution of $LiBHEt_3$ (1.3 mL, 1.3 mmol) was added dropwise over 30 s. The reaction was stirred 15 min and was removed from the cold bath. After warming to rt (15 min), the reaction was quenched with saturated aqueous NH_4Cl (1 mL). The resulting mixture was diluted with Et_2O (20 mL) and H_2O (20 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated to a crude residue. Purification by silica gel chromatography (0% to 10% EtOAc in hexanes) provided 133 mg of a mixture of diastereomers **(±)-D12-3** and **(±)-D12-4.** The combined material from two experiments (253 mg) was further purified by silica gel chromatography (0% to 15% EtOAc in hexanes) to provide **(±)-D12-3** (150 mg) and **(±)-D12-4** (58 mg) as colorless oils. ^{1}H NMR for **(±)-D12-3** (300 MHz, $CDCl_3$) δ 5.91 - 5.69 (m, 1 H), 5.07 - 4.88 (m, 2H), 3.97 (d, *J* = 6.7 Hz, 1 H), 2.19 - 1.99 (m, 3H), 1.84 - 1.73 (m, 1 H), 1.62 (d, *J* = 14.1 Hz, 1 H), 1.54 - 1.40 (m, 2H), 1.32 - 1.17 (m, 3H), 1.16 - 1.06 (m, 1 H), 0.60 - 0.43 (m, 2H). ^{1}H NMR for **(±)-D12-4** (300 MHz, $CDCl_3$) δ 5.95 - 5.73 (m, 1 H), 5.09 - 4.88 (m, 2H), 4.05 - 3.86 (m, 1 H), 2.17 - 1.84 (m, 4H), 1.72 - 1.34 (m, 5H), 1.28 - 1.08 (m, 3H), 0.49 - 0.36 (m, 1H), 0.21 - 0.11 (m, 1 H).

Step 4: Preparation of diastereomeric Intermediate mixture **D12** and **D13:** A mixture of **(±)-D12-3** (150 mg, 0.90 mmol) was dissolved in DMF (1.0 mL). Pyridine (75 µL, 0.92 mmol) and DSC (302 mg, 1.18 mmol) were added, and the reaction was stirred at 45 °C for 21.5 h. The reaction was then placed in an ice water bath and H_2O (1.0 mL) was added dropwise via syringe over 1 min. The mixture was removed from the cold bath and allowed to stir 5 min. The mixture was re-cooled in an ice water bath and L-tert-leucine (154 mg, 1.17 mmol) was added followed by K_3PO_4 (502 mg, 2.36 mmol). The reaction mixture was removed from the cold bath and allowed to stir at rt for 24 h. The mixture was then diluted with EtOAc (40 mL) and 1 M aqueous HCl (20 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (30 mL). The combined organic phase was washed with 0.2 M aqueous HCl (2 x 20 mL), dried over $MgSO_4$, filtered, and concentrated to afford diastereomeric Intermediate mixture **D12** and **D13** (300 mg) as a colorless oil. LCMS-ESI$^-$ (*m/z*): $[M-H]^-$ calcd for $C_{18}H_{28}NO_4$: 322.2; found: 322.0).

Preparation of Intermediate D12.

[0156]



Step 1: Preparation of **D12-5:** To a solution of (1S,4R)-cis-4-acetoxy-2-cyclopent-1-ol (Aldrich, 10 g, 70.4 mmol), triethylamine (48.8 mL, 350 mmol), and DMAP (4.29 g, 35.2 mmol) in dichloromethane (352 mL) was added pivaloyl chloride (10.8 mL, 87.75 mmol) dropwise via syringe at 0 °C under an argon atmosphere. After 2 h, the reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (500 mL), and extracted with dichloromethane (2 × 500 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated *in vacuo* to afford **D12-5** (15.0 g) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (br s, 2H), 5.54 (td, *J* = 8.0, 4.1 Hz, 2H), 2.88 (dt, *J* = 14.9, 7.5 Hz, 1 H), 2.07 (s, 3H), 1.69 (dt, *J* = 14.7, 4.1 Hz, 1 H), 1.20 (s, 9H). Step 2: Preparation of **D12-6:** To a solution of **D12-5** (15.0 g, 70.4 mmol) in methanol (352 mL) was added potassium carbonate (9.73 g, 70.4 mmol) at rt under an argon atmosphere. After 5 h, the reaction mixture was filtered and was concentrated *in vacuo*. The residue was dissolved into ethyl acetate (500 mL) and the resulting mixture was washed with water (500 mL) and brine (500 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes) to afford **D12-6** (12.0 g) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (br d, *J* = 5.5 Hz, 1 H), 5.97 (br d, *J* = 5.6 Hz, 1H), 5.48 (br s, 1H), 4.73 (br s, 1H), 2.82 (dt, *J* = 14.6, 7.3 Hz, 1H), 1.67 (s, 1H), 1.61 (dt, *J* = 14.5, 4.0 Hz, 1H), 1.20 (s, *J* = 3.8 Hz, 9H).

Step 3: Preparation of **D12-7:** To a solution of copper(I) cyanide (5.10 g, 57.0 mmol) in diethyl ether (95 mL) was added pent-4-enylmagnesium bromide (Novel Chemical Solutions, 0.5 M in THF, 114 mL, 57.0 mmol) dropwise via cannula over a 30 min period at 0 °C under an argon atmosphere. After 10 min, a solution of **D12-6** (3.50 g, 19.0 mmol) in diethyl ether (10 mL) was added slowly via cannula. The reaction mixture was then allowed to slowly warm to rt. After 16 h, the resulting mixture was quenched with saturated aqueous ammonium chloride solution (400 mL) and the resulting mixture was extracted into ethyl acetate (2 × 400 mL). The combined organic phases were washed with brine (400 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes) to afford **D12-7** (2.4 g) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1 H), 5.69 (dd, *J* = 5.8, 1.7 Hz, 1H), 5.65 (d, *J* = 7.2 Hz, 1H), 5.00 (dd, *J* = 17.1, 1.3 Hz, 1H), 4.94 (d, *J* = 10.2 Hz, 1H), 4.12 - 4.05 (m, 1H), 2.69 (ddd, *J* = 17.2, 6.4, 1.5 Hz, 1H), 2.54 - 2.45 (m, 1 H), 2.24 (d, *J* = 17.2 Hz, 1 H), 1.69 (br s, 1 H), 1.52 - 1.19 (m, 6H).

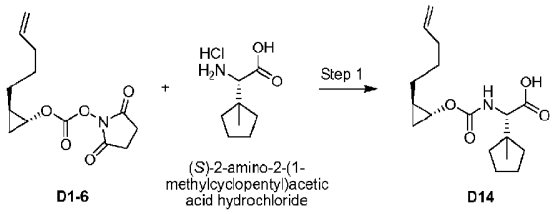
Step 4: Preparation of **(1S,2R,3R,5S)-D12-3:** To a solution of **D12-7** (20 mg, 0.13 mmol), and diethyl zinc (1 M in hexanes, 132 µL, 0.132 mmol) in diethyl ether (0.66 mL) was added diiodomethane (21 µL, 0.26 mmol) at rt under an argon atmosphere. After 2 h, the reaction mixture was quenched with 1 N aqueous HCl solution (0.66 mL). After 5 min, the resulting yellow mixture was diluted with saturated aqueous sodium bicarbonate solution (5 mL) and the resulting mixture was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate solution, and were concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes) to afford **(1S,2R,3R,5S)-D12-3** (10 mg) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1 H), 5.02 (d, *J* = 17.2 Hz, 1 H), 4.96 (d, *J* = 11.3 Hz, 1 H), 4.00 (d, *J* = 6.7 Hz, 1 H), 2.19 - 2.02 (m, 3H), 1.82 (t, *J* = 7.2 Hz, 1 H), 1.64 (d, *J* = 14.2 Hz, 1 H), 1.55 - 1.42 (m, 2H), 1.38 - 1.20 (m, 4H), 1.19 - 1.08 (m, 1 H), 0.62 - 0.47 (m, 2H).

Step 5: Preparation of Intermediate **D12:** Alcohol **(1S,2R,3R,5S)-D12-3** (0.450 g, 2.7 mmol) was taken up in DMF (2.7 mL) and treated subsequently with DSC (0.92 g, 3.52 mmol) and pyridine (0.22 mL, 2.8 mmol). The reaction was then heated to 50 °C o/n. The reaction was then cooled to 0 °C and water (5.5 mL) was added dropwise over 1 min. The resulting opaque suspension was stirred at rt for 10 min before recooling to 0 °C. The reaction was then treated subsequently with L-tert-leucine (0.462 g, 3.5

mmol) and K_3PO_4 (1.5 g, 7.0 mmol) and allowed to warm to rt overnight with vigorous stirring. The resulting opaque suspension was diluted with EtOAc and 1 M aqueous HCl. Additional HCl (12 M) was added dropwise to adjust the pH ~ 3. The aqueous layer was extracted with EtOAc and the combined organics were washed with brine and dried over anhydrous $MgSO_4$. Following concentration *in vacuo,* Intermediate **D12** was obtained (1.72 g) as a viscous, colorless oil that is contaminated with small amounts of DMF and EtOAc. The material was used in subsequent reactions without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{18}H_{30}NO_4$: 324.2; found 324.7.

Preparation of Intermediate D14.

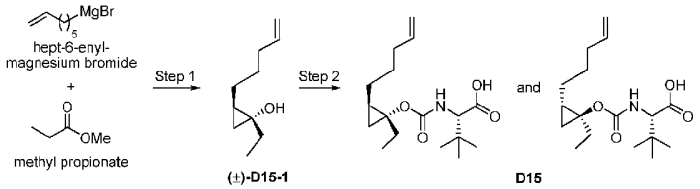
[0157]



[0158] Step 1. Preparation of Intermediate **D14.** Carbonate **D1-6** (862 mg, 3.23 mmol) was treated with (S)-2-amino-2-(1-methylcyclopentyl)acetic acid hydrochloride (750 mg, 3.87 mmol; prepared according to Robl, J.A., et al. J. Med. Chem., 2004, 47, 2587), THF (28 mL), H_2O (8.4 mL) and TEA (1.4 mL, 9.7 mmol). The reaction mixture was stirred for 16 h and the THF was removed *in vacuo.* The remaining material was diluted with H_2O and the pH adjusted to ~10-12 by addition of 10% aqueous NaOH. The aqueous phase was washed twice with EtOAc and then acidified to pH ~ 1-2 with 10% aqueous HCl. The acidic solution was extracted 3x with EtOAc. The combined extractions were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* The initial EtOAc washings (of the basic aqueous solution) were washed with 10% aqueous HCl, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The combined concentrates were purified by silica gel chromatography (50% to 100% EtOAc/Hex) to afford Intermediate **D14** (980 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{28}NO_4$: 310.2; found 310.0.

Preparation of Intermediate mixture D15.

[0159]



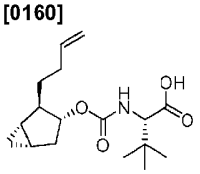
Step 1. Preparation of **(±)-D15-1:** To a solution of titanium(IV) isopropoxide (11.3 g, 40.0 mmol) in THF (160 mL) was added methyl magnesium bromide (3 M in Et_2O, 20 mL, 60.0 mmol) dropwise via syringe at rt under an argon atmosphere. After 10 min, the reaction mixture was cooled to 0 °C and a solution of methyl propionate (3.80 mL, 40.0 mmol) in THF (10 mL) was added slowly via syringe. After 5 min, hept-6-enylmagnesium bromide (Novel Chemical Solutions, 0.5 M in THF, 160 mL, 80 mmol) was added dropwise via addition funnel over 1 h. After 2.5 h, the reaction mixture was quenched with 10% aqueous sulfuric acid (100 mL) and the resulting mixture was extracted with diethyl ether (2 × 200 mL). The organic phase was dried over anhydrous sodium sulfate and was concentrated *in vacuo.* The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes) to afford **(±)-D15-1** (3.03 g, 50%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1 H), 5.03 - 4.86 (m, 2H), 2.04 (q, *J* = 6.1 Hz, 2H), 1.75 - 1.14 (m, 6H), 1.04 (t, *J* = 7.4 Hz, 3H), 1.01 - 0.91 (m, 1 H), 0.89 - 0.71 (m, 2H), 0.02 (t, *J* = 5.5 Hz, 1 H).

Step 2. Preparation of diastereomeric Intermediate mixture **D15:** Racemic alcohol mixture **(±)-D15-1** (2.00 g, 13.0 mmol) was dissolved in DMF (13.0 mL). Pyridine (1.05 mL, 13.0 mmol) was added followed by DSC (4.00 g, 15.6 mmol). The reaction mixture

was heated to 50 °C and was stirred for 20 h. The reaction mixture was then cooled to rt and water (13 mL) was added dropwise over 2 min. L-tert-leucine (2.17 g, 13.0 mmol) and K_3PO_4 (8.28 g, 39.0 mmol) were then added and the reaction mixture was warmed to 50 °C. After 5 h, the reaction mixture was allowed to cool to rt and was diluted with water (500 mL). The resulting mixture was washed with dichloromethane (100 mL). The aqueous phase was then acidified to pH 2 with 2 N aqueous HCl solution, and was extracted with DCM (2 × 400 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated under reduced pressure to afford diastereomeric Intermediate mixture **D15** (4.5 g) as a pale orange oil, which was used subsequently without further purification.

Preparation of Intermediate D16:

[0160]

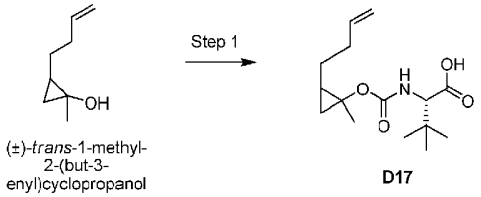


D16

[0161] Intermediate **D16** was prepared in a similar fashion to the preparation of Intermediate **D12,** substituting but-3-enylmagnesium bromide for pent-4-enylmagnesium bromide in Step 3. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{28}NO_4$: 310.2; found 310.8.

Preparation of Intermediate D17:

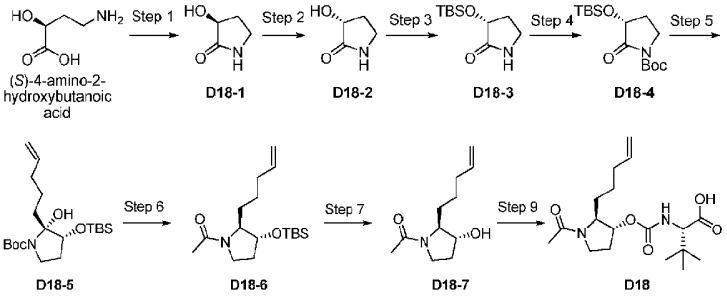
[0162]



[0163] Step 1. Preparation of intermediate mixture **D17.** (±)-trans-1-methyl-2-(but-3-enyl)cyclopropanol (900 mg, .13 mmol), prepared according to procedure for Intermediate B2, International Patent Publication No. WO 2012/40040 (hereinafter "WO '040"), p. 38, was dissolved in DMF (6 mL). Pyridine (577 µL, 7.13 mmol) was added followed by DSC (2.37 g, 9.27 mmol). The reaction mixture was heated to 40 °C and was stirred for 18 h. The reaction mixture was then cooled to 0 °C and water (6 mL) was added dropwise over 5 min. The reaction mixture was stirred for 5 min and was removed from the cold bath. After an additional 5 min, the reaction mixture was cooled to 0 °C and L-tert-leucine (1.21 g, 9.27 mmol) and K_3PO_4 (4.69 g, 22.1 mmol) were added. The mixture was stirred for 10 min and was removed from the cold bath. After stirring an additional 6 h, the mixture was diluted with EtOAc (30 mL), acidified with 1 M aqueous HCl (25 mL), and diluted with 0.2 M aqueous HCl (25 mL). The phases were separated, and the organic phase was washed with 0.2 M aqueous HCl (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated to afford diastereomeric carbamate mixture **D17** (2.10 g). LCMS-ESI$^+$ (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{25}NNaO_4$: 306.2; found: 306.1.

Preparation of Intermediate D18:

[0164]



Step 1. Preparation of **D18-1:** (Prepared according to WO2011013141) To a solution of (S)-4-amino-2-hydroxybutanoic acid (15 g, 126 mmol) in methanol (95 mL) was added concentrated sulfuric acid (8 mL), and the reaction was heated to reflux. After 18 h, the resulting mixture was allowed to cool to room temperature and was concentrated *in vacuo*. The residue was slurried with ethyl acetate (95 mL) and **D18-1** was collected by vacuum filtration. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (br s, 1 H), 4.31 (ddd, *J* = 9.2, 8.1, 2.2 Hz, 1 H), 3.49 (d, *J* = 5.6 Hz, 1 H), 3.41 (tt, *J* = 9.2, 1.7 Hz, 1 H), 3.33 (td, J = 9.4, 6.5 Hz, 1 H), 2.81 (br s, 1 H), 2.59 - 2.48 (m, 1 H), 2.09 (dq, *J* = 12.9, 9.1 Hz, 1 H).

Step 2. Preparation of **D18-2:** To a solution of **D18-1** (4.5 g, 44 mmol), 4-nitrobenzoic acid (8.19 g, 49 mmol), and triphenylphosphine (22.4 g, 132 mmol) in tetrahydrofuran (220 mL) was added diisopropyl azodicarboxylate (12.1 mL, 61.6 mmol) dropwise via syringe at 23 °C under an argon atmosphere. After 20 h, the resulting cloudy orange reaction mixture was concentrated *in vacuo* and methanol (200 mL) followed by potassium carbonate (15 g, 109 mmol) were added and the reaction was stirred at 23 °C. After an additional 5 h, the resulting mixture was diluted with chloroform (200 mL) and was filtered. The filtrate was concentrated *in vacuo* and the crude residue was taken up into water (150 mL) and 1 N aqueous hydrochloric acid solution (50 mL). The aqueous layer was washed with ethyl acetate (3 × 200 mL) to remove organic by-products, and was concentrated *in vacuo* to crude afford **D18-2** that was used directly in the next step. ^{1}H NMR (300 MHz, CD_3OD) δ 4.28 (t, *J* = 8.4 Hz, 1 H), 3.43 - 3.20 (m, 1 H), 2.56 - 2.39 (m, 1 H), 1.96 (dq, *J* = 12.7, 8.7 Hz, 1 H).

Step 3. Preparation of **D18-3:** To a solution of crude **D18-2** (5 g, 49.5 mmol) and imidazole (3.4 g, 49.5 mmol) in DMF (247 mL) was added TBSCl (7.5 g, 49.5 mmol) at 0 °C under an argon atmosphere. The resulting mixture was allowed to warm to 23 °C. After 7 h, additional imidazole (7 g, 102 mmol) and TBSCl (16 g, 106 mmol) were added sequentially. After an additional 16 h, the resulting mixture was diluted with 1 N aqueous hydrochloric acid solution (1 L) and was extracted with ethyl acetate (1 L). The organic layer was split and was washed with brine (1 L), was dried with anhydrous sodium sulfate, and was concentrate *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford **D18-3.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (s, 1 H), 4.26 (t, *J* = 7.7 Hz, 1 H), 3.44 - 3.33 (m, 1 H), 3.30 - 3.19 (m, 1 H), 2.45 - 2.29 (m, 1 H), 2.11 - 1.95 (m, 1 H), 0.91 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H).

Step 4. Preparation of **D18-4:** To a solution of **D18-3** (1.00 g, 4.65 mmol), DMAP (57.8 mg, 0.465 mmol), and triethylamine (1.29 mL, 9.3 mmol) in dichloromethane (23.3 mL) was added di-*tert*-butyl dicarbonate (1.5 g, 6.97 mmol) at 23 °C under and argon atmosphere. After 20 h, the reaction mixture was purified directly by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford **D18-4.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (dd, *J* = 9.4, 7.9 Hz, 1 H), 3.79 (ddd, *J* = 11.0, 8.9, 2.2 Hz, 1 H), 3.53 - 3.41 (m, 1 H), 2.34 - 2.21 (m, 1 H), 1.92 (dq, *J* = 12.2, 9.2 Hz, 1 H), 1.53 (s, 9H), 0.91 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H).

Step 5. Preparation of **D18-5:** To a solution of **D18-4** (700 mg, 2.22 mmol) in tetrahydrofuran (11.1 mL) was added pent-4-enylmagnesium bromide (Novel Chemical Solutions, 0.5 M in 2-MeTHF, 4.89 mL, 2.44 mmol) at -78 °C dropwise via syringe under an argon atmosphere. After 1 h, the reaction mixture was quenched with saturated aqueous ammonium chloride solution (50 mL) and was allowed to warm to room temperature. The resulting mixture was extracted with ethyl acetate (2 × 100 mL), and the combined organic extracts were washed with brine (100 mL), were dried over anhydrous sodium sulfate and were concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford **D18-5.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 - 5.62 (m, 1 H), 4.95 (d, *J* = 15.8 Hz, 1 H), 4.92 (d, *J* = 10.2 Hz, 1 H), 4.26 (app t, *J* = 8.4 Hz, 1 H), 3.77 - 3.69 (m, 1 H), 3.41 (td, *J* = 10.4, 6.7 Hz, 1H), 2.48 (t, *J* = 7.4 Hz, 2H), 2.28 - 2.17 (m, 1 H), 1.91 - 1.78 (m, 2H), 1.77 - 1.65 (m, 1 H), 1.60 (quin, *J* = 7.3 Hz, 2H), 1.47 (s, 9H), 0.85 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H).

Step 6. Preparation of **D18-6:** To a solution of **D18-5** (740 mg, 1.92 mmol) and triethylsilane (6.10 mL, 38.4 mmol) in dichloromethane (9.6 mL) was added boron trifluoride diethyl etherate (308 µL, 2.50 mmol) at -78 °C dropwise via syringe under an argon atmosphere. After 1 h, the reaction mixture was allowed to warm to room temperature. After an additional 4 h, the reaction was quenched with saturated aqueous ammonium chloride solution (10 mL), and was diluted with saturated sodium bicarbonate solution (50 mL). The resulting mixture was extracted with ethyl acetate (50 mL), and the organic layer was dried over

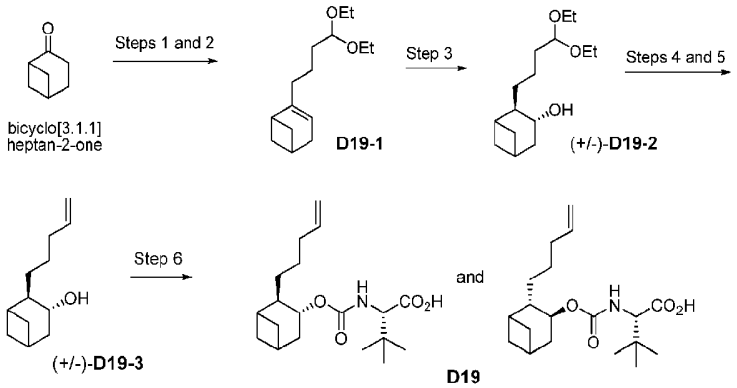
anhydrous sodium sulfate and was concentrated *in vacuo* to afford crude free amine which was used directly in the next step. To a solution of the crude free amine, and triethylamine (535 µL, 3.84 mmol) in tetrahydrofuran (9.6 mL) was added acetic anhydride (146.5 µL, 1.55 mmol) at room temperature under an argon atmosphere. After 1 h, the resulting mixture was concentrated *in vacuo* and the crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford **D18-6** (2:1 diastereomeric mixture favoring desired 1-((2S,3R)-3-(tert-butyldimethylsilyloxy)-2-(pent-4-enyl)pyrrolidin-1-yl)ethanone diastereomer). ^{1}H NMR (400 MHz, $CDCl_3$, Minor diastereomer denoted by *) δ 5.80 - 5.64 (m, 1 H, 1H*), 5.01 - 4.82 (m, 2H, 2H*), 4.10 (d, *J* = 4.2 Hz, 1H*), 4.04 (d, *J* = 3.7 Hz, 1 H), 3.82 (dd, *J* = 10.3, 4.0 Hz, 1 H), 3.66 - 3.56 (m, 1H*), 3.55 - 3.29 (m, 2H, 1H*), 3.24 - 3.16 (m, 1H*), 2.37 - 2.25 (m, 1H*), 2.08 - 1.88 (m, 2H, 1H*), 2.03 (s, 3H*), 2.00 (s, 3H), 1.81 - 1.61 (m, 2H, 2H*), 1.50 - 1.01 (m, 4H, 4H*), 0.85 (s, 9H*), 0.80 (s, 9H), 0.10 (s, 3H*), 0.09 (s, 3H*), 0.00 (br s, 6H).

Step 7. Preparation of **D18-7:** To a solution of **D18-6** (338 mg, 1.08 mmol) in tetrahydrofuran (21 mL) was added TBAF (1 M in tetrahydrofuran, 21 mL, 21 mmol) at 0 °C under an argon atmosphere. After 17 h, the reaction mixture was concentrated *in vacuo* and was directly purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford **D18-7** (102 mg, 2:1 diastereomeric mixture favoring desired 1 1-((2S,3R)-3-hydroxy-2-(pent-4-enyl)pyrrolidin-1-yl)ethanone diastereomer). ^{1}H NMR (400 MHz, $CDCl_3$ Minor diastereomer denoted by *) δ 5.84 - 5.70 (m, 1 H, 1H*), 5.06 - 4.91 (m, 2H, 2H*), 4.25 (d, *J* = 3.7 Hz, 1H*), 4.20 (d, *J* = 3.7 Hz, 1 H), 3.98 (dd, *J* = 9.2, 4.2 Hz, 1 H), 3.76 - 3.68 (m, 1H*), 3.67 - 3.59 (m, 1H, 1H*), 3.55 - 3.46 (m, 1H, 2H*), 3.02 - 2.94 (m, 1 H), 2.22 - 1.85 (m, 2H, 2H*), 2.10 (s, 3H*), 2.07 (s, 3H), 1.82 - 1.59 (m, 2H, 2H*), 1.55 - 1.13 (m, 4H, 4H*).

Step 8. Preparation of **D18-8:** To a solution of **D18-7** (102 mg, 0.518 mmol) and pyridine (8 µL, 0.104 mmol) was added DSC (159.2 mg, 0.621 mmol) at room temperature, and the resulting mixture was heated to 45 °C. After 16 h, the reaction mixture was allowed to cool to room temperature and water (518 µL), L-tert-leucine (86.5 mg, 0.518 mmol), and K_3PO_4 (330 mg, 1.55 mmol) were sequentially added, and the resulting mixture was heated to 50 °C. After 6 h, the reaction mixture was allowed to cool to room temperature and was diluted with 1 N aqueous hydrochloric acid solution (10 mL). The resulting mixture was extracted with dichloromethane (2 × 10 mL), and the combined organic extracts were dried over anhydrous sodium sulfate and were concentrated *in vacuo* to afford **D18-8** (2:1 diastereomeric mixture favoring the desired (S)-2-(((2S,3R)-1-acetyl-2-(pent-4-enyl)pyrrolidin-3-yloxy)carbonylamino)-3,3-dimethylbutanoic acid). ^{1}H NMR (400 MHz, $CDCl_3$, Minor diastereomer denoted by *) δ 5.85 - 5.65 (m, 1H, 1H*), 5.39 (d, *J* = 9.3 Hz, 1H*), 5.34 (d, *J* = 9.2 Hz, 1 H), 5.07 - 4.87 (m, 3H, 3H*), 4.16 - 4.03 (m, 1H, 1H*), 3.83 - 3.45 (m, 3H, 3H*), 2.30 - 1.95 (m, 8H), 2.30 - 1.95 (m, 2H, 3H*), 1.82 - 1.65 (m, 2H, 1H*), 2.11 (s, 3H), 2.09 (s, 3H*), 1.58 - 1.13 (m, 4H, 4H*), 1.01 (br s, 9H, 9H*).

Preparation of Intermediate mixture D19.

[0165]



Steps 1 and 2: Preparation of **D19-1:** A 1.0 M THF solution of KHMDS (10 mL, 10 mmol) was diluted with THF (10 mL) under Ar and the resulting solution was cooled to -78 °C in a CO_2:acetone bath. Bicyclo[3.1.1]heptan-2-one (1.0 g, 9.1 mmol, see: Yin, et. al. J. Org. Chem. 1985, 50, 531) was added as a solution in THF (5 mL) over 2 min, washing with additional THF (2 x 2.5 mL) to ensure complete transfer. The resulting mixture was stirred for 30 min, and *N*-(5-Chloro-2-pyridyl)bis(trifluoromethanesulfonimide) (3.8 g, 9.7 mmol) was added as a solution in THF (10 mL) over 2 min, washing with additional THF (2 x 2.5 mL). The resulting mixture was stirred for 5 min and removed from the cold bath. After stirring an additional 30 min, the reaction was diluted with Et_2O (70 mL) and 1 M aqueous HCl (50 mL). The phases were separated, and the organic phase was washed with 1 M aqueous NaOH (2 x 30 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated to afford a crude residue. This

was filtered through a plug of silica with 30% EtOAc in hexanes to afford a crude residue of (1.24 g) that was used directly in the following step. Step 2: To a solution of 3-butenal diethyl acetal (1.4 mL, 8.3 mmol) under Ar cooled in an ice water bath was added a 0.5 M THF solution of 9-borabicyclo[3.3.1]nonane (15.9 mL, 7.95 mmol) over 3 min. The reaction was stirred for 20 h, with the cold bath being allowed to expire overnight. A 3 M aqueous solution of NaOH (2.9 mL, 8.7 mmol) was then added, and, after stirring 20 min, the resulting solution was transferred in its entirety to a flask containing the product from Step 1 (ca. 5.16 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (420 mg, 0.51 mmol). The resulting mixture was heated to 60 °C. After stirring 14 h, the reaction mixture was diluted with Et_2O (50 mL) and H_2O (50 mL). The phases were separated, and the organic phase was dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (0% to 10% EtOAc in hexanes following pre-equilibration with 1% Et_3N in EtOAc) provided intermediate **D19-1.** ^1H NMR (300 MHz, $CDCl_3$) 5.36 - 5.28 (m, 1 H), 4.59 (t, *J* = 5.6 Hz, 1 H), 3.73 - 3.58 (m, 2H), 3.54 - 3.39 (m, 2H), 2.72 - 2.60 (m, 1 H), 2.45 - 2.34 (m, 3H), 2.23 - 2.08 (m, 4H), 1.89 - 1.76 (m, 2H), 1.67 (dt, *J* = 16.1, 6.9 Hz, 2H), 1.58 - 1.47 (m, 2H), 1.23 (t, *J* = 7.0 Hz, 6H).

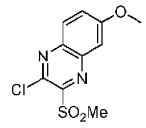
Step 3: Preparation of **D19-2:** A solution of olefin **D19-1** (660 mg, 2.77 mmol) in THF (25 mL) was cooled in an ice water bath. $BH_3\cdot Me_2S$ was then added as a 1 M solution in CH_2Cl_2 (2.9 mL, 2.9 mmol) over 1 min. The resulting solution was stirred for 2 h in the ice water bath and was then allowed to warm to r.t. After stirring an additional 3 h, the reaction mixture was re-cooled in an ice water bath and was diluted with 2 M aqueous NaOH (7 mL) followed by 30 % aqueous H_2O_2 (7 mL). The resulting mixture was stirred an additional 16 h as the cold bath was allowed to gradually expire. The mixture was partitioned between Et_2O (100 mL) and H_2O (50 mL), the phases were separated, and the organic phase was washed with 0.5 M aqueous NaOH (50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to afford a crude residue that was purified by silica gel chromatography (15% to 40% EtOAc in hexanes) to afford 570 mg of Intermediate **D19-2.** ^1H NMR (300 MHz, $CDCl_3$) δ 4.60 (t, *J* = 5.6 Hz, 1 H), 3.76 - 3.60 (m, 3H), 3.58 - 3.42 (m, 2H), 2.39 - 2.05 (m, 4H), 1.91 - 1.48 (m, 9H), 1.43 - 1.35 (m, 1 H), 1.25 (t, *J* = 7.0 Hz, 6H), 1.06 - 0.98 (m, 1 H).

Steps 4 and 5: Preparation of **D19-3:** Acetal **D19-2** (360 mg, 1.4 mmol) was dissolved in THF (8 mL) and H_2O (2 mL). *para*-Toluenesulfonic acid monohydrate (40 mg, 0.2 mmol) was added and the resulting solution was stirred 16 h at r.t. The reaction was diluted with Et_2O (50 mL) and H_2O (30 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (30 mL) and the combined organic phase was washed with saturated aqueous $NaHCO_3$ (15 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to afford a crude residue that was used immediately in the following step. Step 5: Methyl triphenylphosphonium bromide (1.66 g, 4.6 mmol) was suspended in THF (40 mL) under Ar and was cooled via a CO_2/aceton bath to -78 °C. A 1 M solution of NaHMDS in THF (4.2 mL, 4.2 mmol) was added in dropwise fashion and the resulting yellow suspension was stirred for 5 min. The mixture was removed from the cold bath and stirring continued an additional 30 min. The mixture was then re-cooled to -78 °C and the crude residue from the previous step (ca. 1.4 mmol) was added as a solution in THF (5 mL) over 5 min, washing with additional THF (2 x 2.5 mL) to ensure complete transfer. The resulting mixture was stirred for 5 min and was then placed in an ice water bath and stirred an additional 1 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and was diluted with Et_2O (30 mL) and H_2O (20 mL). The phases were separated and the organic phase was dried over $MgSO_4$, filtered, and concentrated onto 5 g silica gel. Purification by silica gel chromatography (10% to 30% EtOAc in hexanes) provided **D19-3.** ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 - 5.81 (m, 1 H), 5.22 - 5.05 (m, 2H), 3.79 - 3.66 (m, 1 H), 2.43 - 2.25 (m, 2H), 2.24 - 2.04 (m, 4H), 1.83 - 1.16 (m, 10H).

Step 6: Intermediate **D19-3** (270 mg, 1.5 mmol) was dissolved in DMF (2.0 mL). Pyridine (125 µL, 1.5 mmol) and DSC (500 mg, 1.9 mmol) were added, and the reaction was stirred at 45 °C for 15 h. The reaction was then placed in an ice water bath and H_2O (2.0 mL) was added dropwise over 30 s. The mixture was removed from the cold bath and allowed to stir 10 min. The mixture was re-cooled in an ice water bath and L-*tert*-leucine (259 mg, 1.97 mmol) was added followed by K_3PO_4 (835 mg, 3.93 mmol). The reaction mixture was removed from the cold bath and allowed to stir at r.t. for 5.25 h. The mixture was then diluted with EtOAc (40 mL), 1 M aqueous HCl (20 mL), and H_2O (15 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (30 mL). The combined organic phase was washed with 0.2 M aqueous HCl (2 x 25 mL), dried over Na_2SO_4, filtered, and concentrated to afford a mixture of diastereomers **D19** (505 mg) as a colorless oil. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{19}H_{32}NO_4$: 338.2; found: 337.8.

Preparation of Intermediate E1.

[0166]



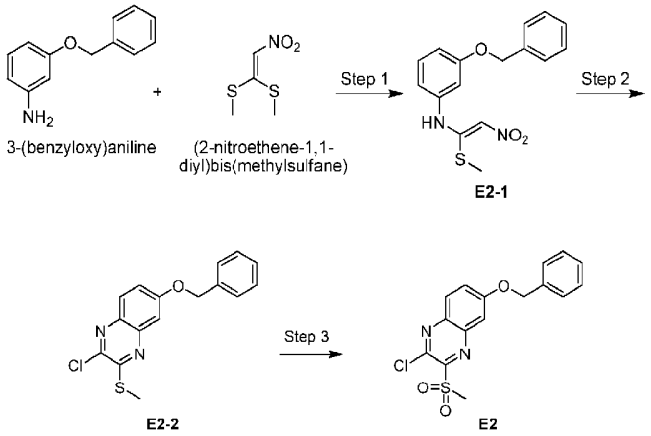
2-chloro-6-methoxy-3-(methylsulfonyl)quinoxaline

E1

[0167] Intermediate **E1** (2-chloro-6-methoxy-3-(methylsulfonyl)quinoxaline) was prepared according to Mahata, P.K., et al. Org. Lett. 2005, 7, 2169.

Preparation of Intermediate E2.

[0168]



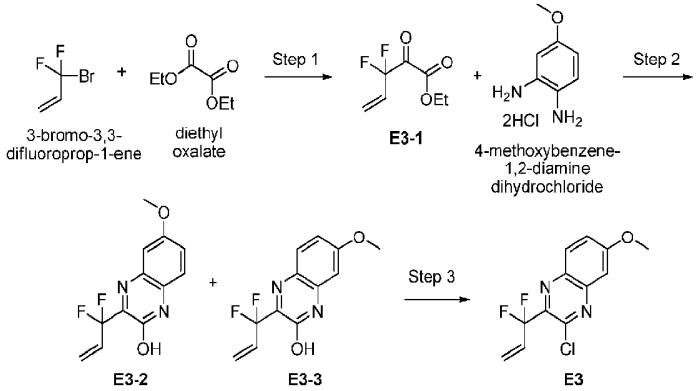
Step 1. Preparation of **E2-1:** In a round bottom flask, 3-(benzyloxy)aniline (4.025 g, 20.20 mmol) and 1,1-bis(methylthio)-2-nitroethylene (3.338 g, 20.20 mmol) in ethanol (40 mL) was refluxed for 24 h with constant stirring. The reaction mixture was then cooled in an ice bath and diluted with ether (150 mL). The mixture was filtered and washed with ether to afford **E2-1** (3.32 g) as a yellow solid which was used directly in the following in step. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{17}N_2O_3S$: 317.1; found: 317.1.

Step 2. Preparation of **E2-2:** To a suspension of **E2-1** (3.32 g, 10.49 mmol) in 25 mL MeCN, $POCl_3$ (2.93 mL, 31.5 mmol) was added dropwise over 15 min with constant stirring. The reaction mixture was warmed to 80 °C and stirred for 5 h. The reaction was then cooled to ambient temperature and neutralized with ice cold saturated aqueous $NaHCO_3$ solution, extracted three times with CH_2Cl_2(100 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude material was eluted through a plug of silica with CH_2Cl_2. The solvent was removed under reduced pressure and the solid was washed with MeCN to afford **E2-2** (1.56 g) as an off white solid. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{14}ClN_2OS$: 317.1; found: 317.3.

Step 3. Preparation of Intermediate **E2.** A solution of *m*CPBA (1.87 g, 10.83 mmol) in CH_2Cl_2 (40 mL) was added dropwise to a stirred solution of **E2-2** (1.56 g, 4.92 mmol) in CH_2Cl_2 (40 mL) at 0 °C over a period of 30 min. The reaction mixture was further stirred at ambient temperature for 5 h. It was then poured into ice could saturated aqueous $NaHCO_3$ and partitioned with CH_2Cl_2. The organic layer was then washed subsequently with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude material was purified by normal phase chromatography with CH_2Cl_2 to provide the title compound Intermediate **E2** as a pale yellow solid. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{14}ClN_2O_3S$: 349.0; found: 349.0.

Preparation of Intermediate E3.

[0169]



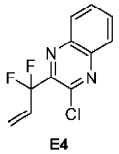
Step 1. Preparation of **E3-1:** To a solution of 3-bromo-3,3-difluoroprop-1-ene (25.0 g, 159 mmol) and diethyl oxalate (21.6 mL, 159 mmol) in THF (380 mL), diethyl ether (90 mL) and *n*-pentane (90 mL) at -100 °C was added dropwise n-butyllithium (2.5 M in hexane, 67 mL, 167.6 mmol) over 30 min. The reaction mixture was stirred at -95 °C for 1 h and -78 °C for 2 h, and quenched with aq. NH_4Cl (11 g in 150 mL of water). The mixture was extracted with ether (three times). The organic layers were washed with 1 N aqueous HCl, brine, and dried over Na_2SO_4, and concentrated to give the crude residue, which was purified by silica gel chromatography (EtOAc in hexanes: 0% to 40%) to give **E3-1** (7.0 g). ^1H NMR (300 MHz, $CDCl_3$) δ 5.98-6.18 (m, 1 H), 5.78 (dd, J = 0.9 Hz, 13 Hz, 1 H), 5.60 (dd, J = 0.9 Hz, 11 Hz, 1 H), 4.38 (q, J = 6.9 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H).

Step 2. Preparation of **E3-2** and **E3-3:** To a solution of **E3-1** (14.0 g, 78.6 mmol) and 4-methoxybenzene-1,2-diamine dihydrochloride (15.08 g, 71.4 mmol) in EtOH (360 mL) at rt was added triethylamine (19.9 mL, 142.8 mmol). The reaction mixture was stirred at rt overnight. The mixture was concentrated. Slurrying in dichloromethane (30 mL) and filtering gave some separation of regioisomers with **E3-2** as the precipitating species. (16.5 g total yield from filtration and subsequent chromatography). ^1H NMR (400 MHz, $CDCl_3$) δ 11.940 (br s, 1 H), 7.850 (d, J = 9 Hz, 1 H), 6.985 (dd, J = 3 Hz, 9 Hz, 1 H), 6.754 (d, J = 2 Hz, 1 H), 6.625-6.498 (m, 1 H), 5.907 (dt, J = 17, 2 Hz, 1 H), 5.601 (d, J = 11 Hz, 1 H), 3.938 (s, 3H). The mixture was slurried, filtered, and concentrated once more, then was purified by silica gel chromatography (EtOAc in hexanes: 5% to 34%) to give **E3-3** (2.07 g) as the first eluting component. ^1H NMR (400 MHz, $CDCl_3$) δ 12.05 (br s, 1 H), 7.850 (d, J = 9 Hz, 1 H), 6.986 (dd, J = 3 Hz, 9 Hz, 1 H), 6.761 (d, J = 3 Hz, 1 H), 6.597-6.526 (m, 1 H), 5.91 (dt, J = 17, 2 Hz, 1 H), 5.601 (d, J = 11 Hz, 1 H), 3.939 (s, 3H).

Step 3. Preparation of Intermediate **E3:** A solution of **E3-3** (2.07 g, 8.2 mmol in 1 mL DMF was treated with $POCl_3$ (0.8 mL) and heated at 65 °C for 2.5 h. The reaction was diluted with EtOAc and quenched by pouring into ice water. The organic phase was washed subsequently with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate and concentrated to give 2.1 g of Intermediate **E3.** ^1H NMR (400 MHz, $CDCl_3$) δ 8.028 (d, J = 10 Hz, 1H), 7.46 (dd, J = 3 Hz, 9 Hz, 1 H), 7.32(d, J = 3 Hz, 1 H), 6.549-6.478 (m, 1 H), 5.86 (dt, J = 17, 2 Hz, 1 H), 5.67 (d, J = 11 Hz, 1 H), 3.981 (s, 3H).

Preparation of Intermediate E4.

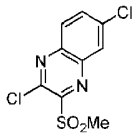
[0170]



[0171] Intermediate **E4** (2-chloro-3-(1,1-difluoroallyl)quinoxaline) was prepared in a similar fashion to Intermediate **E3,** substituting 1,2-diaminobenzene for 4-methoxybenzene-1,2-diamine dihydrochloride in Step 2.

Preparation of Intermediate E5.

[0172]

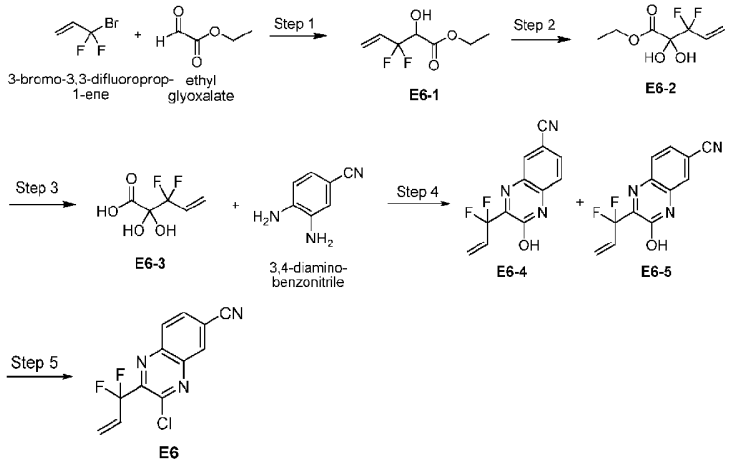


E5

[0173] Intermediate **E5** (2,6-dichloro-3-(methylsulfonyl)quinoxaline) was prepared according to Mahata, P.K., et al. Org. Lett. 2005, 7, 2169.

Preparation of Intermediate E6.

[0174]



Step 1. Preparation of **E6-1:** A 1-L 3-necked round-bottom flask was charged with a solution of 3-bromo-3,3-difluoroprop-1-ene (25 g, 159.3 mmol) in DMF (360 mL) and water (90 mL). The resulting solution was treated with ethyl 2-oxoacetate (33 mL,1 M in toluene), and In (25 g). The reaction mixture was stirred overnight at rt and then extracted with 3x300 mL of ether. The organic layers were combined, washed with 1x100 mL of saturated aqueous NH_4Cl and 1x100 mL of brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford **E6-1** that was used subsequently without additional purification.

Step 2. Preparation of **E6-2.** To hydroxyester **E6-1** (58.1 g, 323 mmol) was added DCM (700 mL) in a 2 L 3-neck flask equipped with overhead stirring and an internal temperature probe. Then TEMPO (5.4 g, 35 mmol), buffer solution (prepared by dissolving 4.2 g $NaHCO_3$ and 0.53 g Na_2CO_3 per 100 mL water, 700 mL, 7v), and NaOCl (Clorox 6.15% wt, 422 mL, 395 mmol) were sequentially added to the flask at 20 °C. After 2 h the organic layer was separated and the aqueous phase extracted with ethyl acetate (2 × 300 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford **E6-2.** ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.98-6.18 (m, 1 H), 5.78 (dd, J = 0.9 Hz, 13 Hz, 1 H), 5.60 (dd, J = 0.9 Hz, 11 Hz, 1 H), 4.38 (q, J = 6.9 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H).

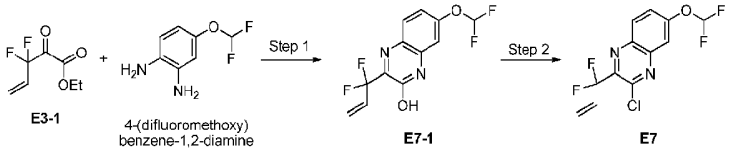
Step 3. Preparation of **E6-3.** To a solution of ethyl 3,3-difluoro-2,2-dihydroxypent-4-enoate **E6-2** (57.4 g, 292 mmol) in THF (725 mL) and water (131 mL) was added $LiOH•H_2O$ (22 g, 529 mmol) at 20 °C. After 2.5 h, the reaction mixture was concentrated *in vacuo.* The solid residue was suspended in water (300 mL) and the resulting mixture was acidified to pH = 1 with concentrated aqueous hydrochloric acid solution. The resulting mixture was stirred until all solids were dissolved (~1.5 h), and then sodium chloride was added until the solution was saturated. The resulting solution was extracted with MTBE (2 × 500 mL) and ethyl acetate (2 × 500 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and were concentrated *in vacuo.* The crude orange solid residue was suspended into DCM (100 mL) and was stirred until the solids were finely distributed before hexanes (75 mL) were slowly added via addition funnel. The resulting solids were collected by vacuum filtration through a medium fritted funnel and washed with 1:1 dichloromethane/ hexanes (2 × 10 mL) to afford the desired product. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 13.17 (bs, 1 H), 6.18-6.01 (m, 1 H), 5.64-5.52 (m, 2H).

Step 4. Preparation of **E6-4** and **E6-5:** A solution of **E6-3** (0.5 g, 3.3 mmol) in EtOH (12 mL) was treated with 3,4-diaminobenzonitrile (0.47 g, 3.5 mmol). The reaction mixture was heated at 80 °C for 1 h, then concentrated *in vacuo*. The resulting residue was absorbed on silica gel, then was purified by column chromatography to give **E6-4** (0.5 g) as the first eluting component. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.01 (d, 1H), 7.65 (dd, 2H), 6.49 (m, 1H), 5.80 (dt, 1H), 5.60 (d, 1H). **E6-5** (0.2 g) was recovered as the second eluting component. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.25 (d, 1 H), 7.87 (dd, 1 H), 7.41 (d, 1 H), 6.49 (m, 1H), 5.80 (dt, 1H), 5.59 (d, 1 H).

Step 5. Preparation of Intermediate **E6:** A solution of **E6-4** (0.5 g, 2 mmol in 4.5 mL DMF was treated with $POCl_3$ (3 mL) and heated at 65 °C for 3 h. The reaction was diluted with EtOAc and quenched by pouring into ice water. The organic phase was washed subsequently with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 0.48 g of Intermediate **E6** (3-chloro-2-(1,1-difluoroallyl)quinoxaline-6-carbonitrile). ^{1}H-NMR (400 MHz, CD_3OD) δ 8.52 (s, 1 H), 8.30 (d, 1 H), 8.13 (dd, 1 H), 6.55 (m, 1 H), 5.84 (dt,1H), 5.72 (d, 1 H).

Preparation of Intermediate E7

[0175]



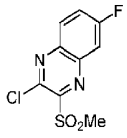
E3-1 | 4-(difluoromethoxy) benzene-1,2-diamine | E7-1 | E7

Step 1. Preparation of **E7-1:** To a solution of **E3-1** (1.84 g, 10.93 mmol) and 4-(difluoromethoxy)benzene-1,2-diamine (1.90 g, 10.93 mmol, prepared according to Reference Example 30y of WO2003035065, p. 511.) in DMF (40 mL) at rt was added DIPEA (9.5 mL, 54.65 mmol) and HATU (6.23 g, 16.4 mmol). The reaction mixture was stirred at room temperature for 24 h, diluted with ethyl acetate (100 mL), washed with water (100 mL) and brine (50 mL). The mixture was concentrated *in vacuo*. Purification via silica gel chromatography (EtOAc in hexanes: 20% to 60%) provided **E7-1** (800 mg) as the later eluting fraction of two with the similar mass spectra. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{12}H_9F_4N_2O$: 289.2; found: 289.0.

Step 2: Preparation of Intermediate **E7:** Hydroxyquinoxaline **E7-1** (800 mg, 2.8 mmol), $POCl_3$ (1.65 mL, 3.0 mmol) and DMF (10 mL) are combined at rt and then heated to 65 °C for 2.5 h at which time additional $POCl_3$ (0.2 mL, 0.36 mmol) was added. The reaction was heated an additional 3 h at 65 °C then cooled to rt. The reaction was quenched by addition of cold water (30 mL), and taken up into ethyl acetate (50 mL), washed with saturated aqueous Na_2CO_3 (100 mL) followed by brine (50 mL), and dried over anhydrous $MgSO_4$. The resulting solution was concentrated *in vacuo* to give Intermediate **E7** (859 mg) which was used subsequently without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{12}H_8ClF_4N_2O$: 307.0; found: 307.0.

Preparation of Intermediate E8.

[0176]

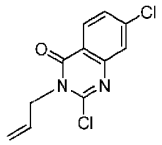


E8

[0177] Intermediate **E8** (2-chloro-6-fluoro-3-(methylsulfonyl)quinoxaline) was prepared according to Mahata, P.K., et al. Org. Lett. 2005, 7, 2169.

Preparation of Intermediate E9.

[0178]



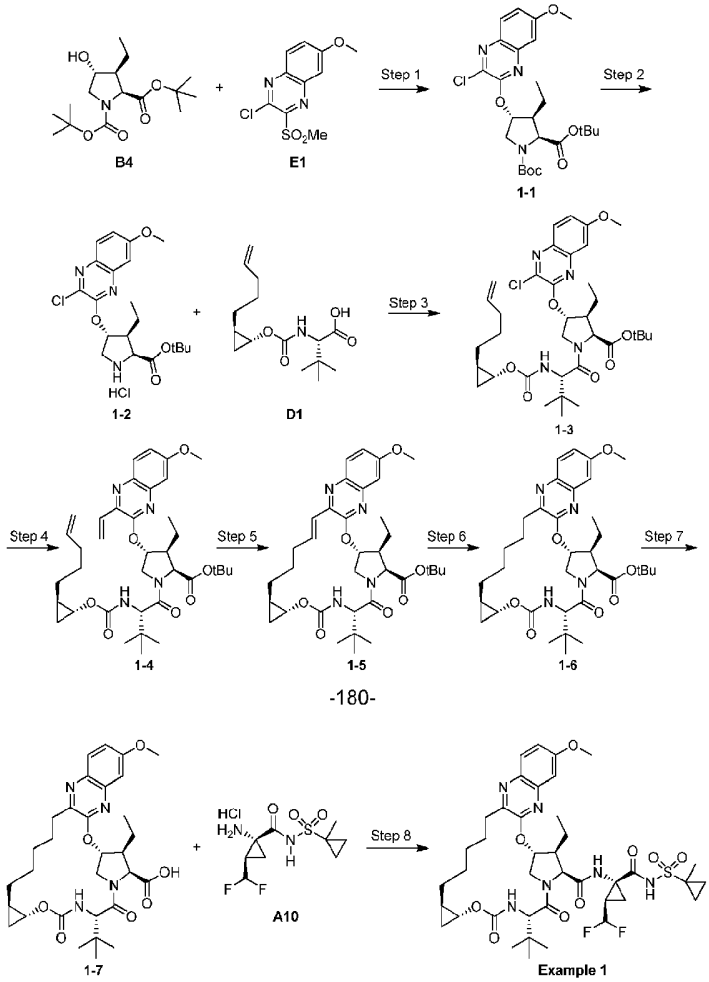
E9

[0179] 2,7-dichloro-3-(prop-2-en-1-yl)quinazolin-4(3H)-one (Intermediate **E9**) was prepared according to Step 3 of Intermediate D5 of WO '040 p 53-4.

Preparation of Examples

[0180] Compounds IVa-IVh are according to the invention. All other compounds are reference examples.

[0181] Example **1.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Step 1. Preparation of **1-1:** A mixture containing Intermediate **B4** (2.03 g, 6.44 mmol), Intermediate **E1** (1.6 g, 5.85 mmol), and cesium carbonate (3.15 g, 9.66 mmol) in MeCN (40 mL) was stirred vigorously at rt under an atmosphere of Ar for 16 h. The reaction was then filtered through a pad of Celite and the filtrate concentrated *in vacuo*. The crude material was purified by silica

gel chromatography to provide **1-1** as a white solid (2.5 g). LCMS-ESI$^+$ (*m/z*): [M-Boc+2H]$^+$ calcd for $C_{20}H_{27}ClN_3O_4$: 408.9; found: 408.6.

Step 2. Preparation of **1-2:** To a solution **1-1** (2.5 g, 4.92 mmol) in dioxane (10 mL) was added hydrochloric acid in dioxane (4 M, 25 mL, 98.4 mmol) and the reaction stirred at rt for 5 h. The crude reaction was concentrated *in vacuo* to give **1-2** as a white solid (2.49 g) that was used in subsequently without further purification. LCMS-ESI$^+$ (*m/z*): [M]$^+$ calcd for $C_{20}H_{26}ClN_3O_4$: 407.9; found: 407.9.

Step 3. Preparation of **1-3:** To a DMF (35 mL) solution of **1-2** (2.49 g, 5.61 mmol), Intermediate **D1** (1.75 mg, 6.17 mmol) and DIPEA (3.9 mL, 22.44 mmol) was added COMU (3.12 g, 7.29 mmol) and the reaction was stirred at rt for 3 h. The reaction was quenched with 5% aqueous citric acid solution and extracted with EtOAc, washed subsequently with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to produce **1-3** as an orange foam (2.31 g) that was used without further purification. LCMS-ESI$^+$ (*m/z*): [M]$^+$ calcd for $C_{35}H_{49}ClN_4O_7$: 673.3; found: 673.7.

Step 4. Preparation of **1-4:** To a solution of **1-3** (2.31 g, 3.43 mmol), TEA (0.72 mL, 5.15 mmol) and potassium vinyltrifluoroborate (0.69 mg, 5.15 mmol) in EtOH (35 mL) was added $PdCl_2$(dppf) (0.25 g, 0.34 mmol, Frontier Scientific). The reaction was sparged with Argon for 15 min and heated to 80 °C for 2 h. The reaction was adsorbed directly onto silica gel and purified using silica gel chromatography to give **1-4** as a yellow oil (1.95 g). LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{37}H_{53}N_4O_7$: 665.4; found: 665.3.

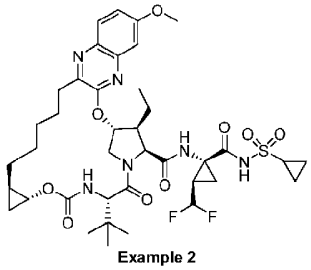
Step 5. Preparation of **1-5:** To a solution of **1-4** (1.95 g, 2.93 mmol) in DCE (585 mL) was added Zhan 1B catalyst (0.215 g, 0.29 mmol, Strem) and the reaction was sparged with Ar for 15 min. The reaction was heated to 80 °C for 1.5 h, allowed to cool to rt and concentrated. The crude product was purified by silica gel chromatography to produce **1-5** as a yellow oil (1.47 g; LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{35}H_{49}N_4O_7$: 637.4; found: 637.3).

Step 6. Preparation of **1-6:** A solution of **1-5** (0.97 g, 1.52 mmol) in EtOH (15 mL) was treated with Pd/C (10 wt % Pd, 0.162 g). The atmosphere was replaced with hydrogen and stirred at rt for 2 h. The reaction was filtered through Celite, the pad washed with EtOAc and concentrated to give **1-6** as a brown foamy solid (0.803 g) that was used subsequently without further purification. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{35}H_{51}N_4O_7$: 639.4; found: 639.3.

Step 7. Preparation of **1-7:** To a solution of **1-6** (0.803 g, 1.26 mmol) in DCM (10 mL) was added TFA (5 mL) and stirred at rt for 3 h. An additional 2 mL TFA was added and the reaction stirred for another 1.5 h. The reaction was concentrated to a brown oil that was taken up in EtOAc (35 mL). The organic solution was washed with water. After separation of the layers, sat. aqueous $NaHCO_3$ was added with stirring until the aqueous layer reached a pH ~ 7-8. The layers were separated again and the aqueous extracted with EtOAc twice. The combined organics were washed with 1 M aqueous citric acid, brine, dried over anhydrous $MgSO_4$, filtered and concentrated to produce **1-6** as a brown foamy solid (0.719 g) that was used subsequently without further purification. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{31}H_{43}N_4O_7$: 583.3; found: 583.4 .

Step 8. Preparation of Example **1:** To a solution of **1-7** (0.200 g, 0.343 mmol), Intermediate **A10** (0.157 g, 0.515 mmol), DMAP (0.063 g, 0.51 mmol) and DIPEA (0.3 mL, 1.72 mmol) in DMF (3 mL) was added HATU (0.235 g, 0.617 mmol) and the reaction was stirred at rt o/n. The reaction was diluted with MeCN and purified directly by reverse phase HPLC (Gemini, 30-100% MeCN/H_2O + 0.1 % TFA) and lyophilized to give Example **1** (118.6 mg) as a solid TFA salt. Analytic HPLC RetTime: 8.63 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{40}H_{55}F_2N_6O_9S$: 833.4; found: 833.5. ^{1}H NMR (400 MHz, CD_3OD) δ 9.19 (s, 1H); 7.80 (d, J= 8.8 Hz, 1H); 7.23 (dd, J = 8.8, 2.4 Hz, 1H); 7.15 (d, J= 2.4 Hz, 1H); 5.89 (d, J= 3.6 Hz, 1H); 5.83 (td, J_{H-F} = 55.6 Hz, J= 6.4 Hz, 1H); 4.56 (d, J = 7.2 Hz, 1H); 4.40 (s, 1H) 4.38 (ap d, J = 7.2 Hz, 1 H); 4.16 (dd, J = 12, 4 Hz, 1H); 3.93 (s, 3H); 3.75 (dt, J= 7.2, 4 Hz, 1H); 3.00-2.91 (m, 1H); 2.81 (td, J = 12, 4.4 Hz, 1H); 2.63-2.54 (m, 1H); 2.01 (br s, 2H); 1.88-1.64 (m, 3H); 1.66-1.33 (m, 11H) 1.52 (s, 3H); 1.24 (t, J= 7.2 Hz, 3H); 1.10 (s, 9H); 1.02-0.96 (m, 2H); 0.96-0.88 (m, 2H); 0.78-0.68 (m, 1 H); 0.55-0.46 (m, 1 H).

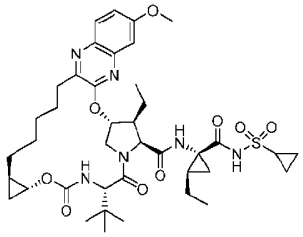
[0182] Example **2.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1 R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-9-ethyl-14-methoxy-3,6-dioxo-1,1 a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 2

[0183] Example **2** was prepared in a similar fashion to Example **1,** substituting Intermediate **A9** for Intermediate **A10** in Step 8. Example **2** was isolated (37.9 mg) in approximately 85% purity as a TFA salt. Analytic HPLC RetTime: 8.54 min. LCMS-ESI $^+$ (*m/z*): $[M+H]^+$calcd for $C_{39}H_{53}F_2N_6O_9S$: 819.35; found: 819.51. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H); 7.90 (d, J = 9.2 Hz, 1H); 7.26 (dd, J = 9.2, 2.4 Hz, 1H); 7.10 (d, J = 2.4 Hz, 1H); 6.68 (br s, 1H); 6.01 (td, J_{H-F} = 55.6 Hz, J = 6.8 Hz, 1H); 5.87 (d, J = 3.6 Hz, 1H); 5.38, (d, J = 10 Hz, 1H); 4.50-4.40 (m, 3H); 4.10 (dd, J = 12, 3.6 Hz, 1 H); 3.95 (s, 3H); 3.79-3.72 (m, 1H); 2.96-2.82 (m, 3H); 2.63-2.56 (m, 1H); 2.14 (t, J = 6.8 Hz, 1H); 1.98-1.86 (m, 1H); 1.84-1.28 (m, 13H); 1.23 (t, J = 7.2 Hz, 3H); 1.16-0.92 (m, 3H); 1.09 (s, 9H); 0.74-0.64 (m, 1H); 0.48 (q, J = 6.4 Hz, 1H).

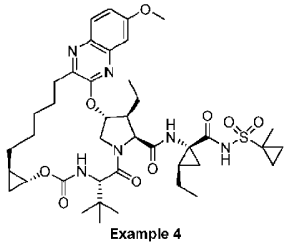
[0184] Example **3.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-{(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethylcyclopropyl}-9-ethyl-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 3

[0185] Example **3** was prepared in a similar fashion to Example **1,** substituting Intermediate **A3** for Intermediate **A10** in Step 8. Example **3** was isolated (0.035 g) in approximately 88% purity as a TFA salt. Analytic HPLC RetTime: 8.63 min. LCMS-ESI $^+$ (m/z): $[M+H]^+$calcd for $C_{40}H_{57}N_6O_9S$: 797.4; found: 797.5. ^{1}H NMR (400 MHz, CD_3OD) δ 8.98 (s, H); 7.80 (d, J = 9.2 Hz, 1H); 7.23 (d, J = 9.2, 2.8 Hz, 1H); 7.15 (d, J = 2.8 Hz, 1H); 5.89 (d, J = 3.6 Hz, 1H); 4.58 (d, J = 7.6 Hz, 1H); 4.41-4.32 (m, 2H); 4.16 (dd, J = 12.4 Hz, 3.6 Hz, 1H); 3.93 (s, 3H); 3.74 (dt, J = 6.8, 2.8 Hz, 1H); 3.20-2.91 (m, 2H); 2.86-2.76 (m, 1H); 2.61-2.53 (m, 1H); 1.88-1.68 (m, 4H); 1.66-1.34 (m, 9H); 1.34-1.20 (m, 5H); 1.18-1.04 (m, 3H); 1.10 (s, 9H); 1.00-0.92 (m, 7H); 0.79-0.69 (m, 1 H); 0.50 (br d, J = 7.2 Hz, 1 H).

[0186] Example **4.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-9-ethyl-N-[(1R,2R)-2-ethyl-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.

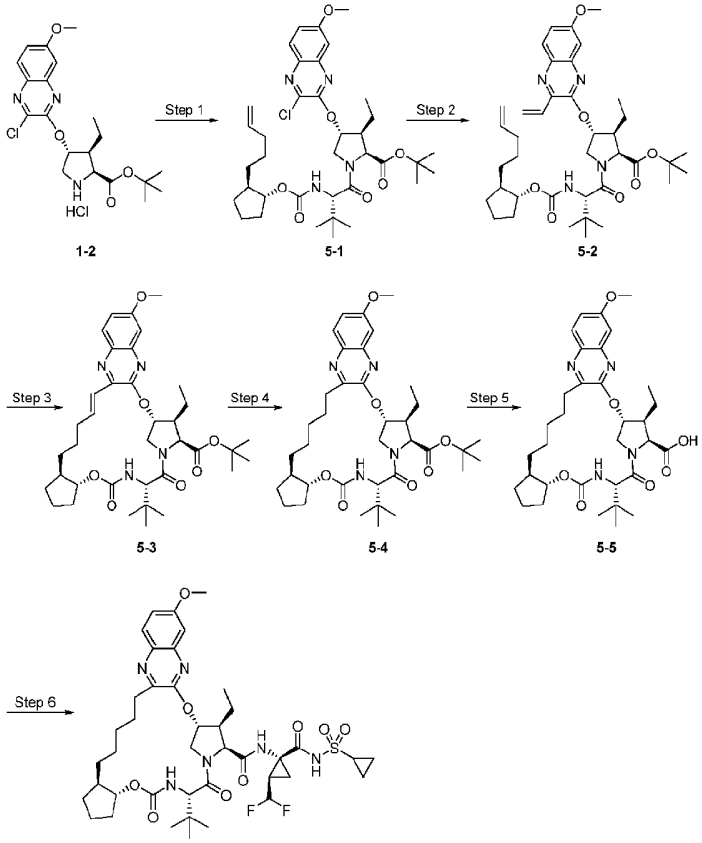


Example 4

[0187] Example **4** was prepared in a similar fashion to Example **1,** substituting Intermediate **A4** for Intermediate **A10** in Step 8. Example **4** was isolated (0.018 g) in approximately 88% purity as a TFA salt. Analytic HPLC RetTime: 8.75. LCMS-ESI $^+$ (*m/z*): $[M+H]^+$ calcd for $C_{41}H_{59}N_6O_9S$: 811.4; found: 811.6. ^{1}H NMR (400 MHz, CD_3OD) δ 8.91 (s, 1H); 7.80 (d, J = 9.2 Hz, 1H); 7.23 (dd,

J = 9.2, 2.8 Hz, 1H); 7.16 (d, J = 2.8 Hz, 1H); 5.90 (d, J = 3.6 Hz, 1H); 4.59 (d, J = 6.8 Hz, 1H); 4.38 (s, 1H); 4.37 (d, J = 11.6 Hz, 1H), 4.16 (dd, J = 11.6, 6.8 Hz, 1H), 3.93 (s, 3H); 3.74 (dt, J = 6.8, 3.6 Hz, 1H); 3.10-2.91 (m, 1H); 2.90-2.7 (m, 1H); 2.63-2.55 (m, 1H); 1.86-1.69 (m, 3H); 1.65-1.36 (m, 13H), 1.52 (s, 3H); 1.24 (t, J = 7.2 Hz, 3H); 1.16-1.06 (m, 2H); 1.10 (s, 9H); 1.02-0.85 (m, 7H); 0.79-0.68 (m, 1H); 0.50 (br d, J = 6.8 Hz, 1H).

[0188] Example **5.** Preparation of (3aR,7S,10S,11S,12R,24aR)-7-tert-butyl-N-[(1 R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-11-ethyl-16-methoxy-5,8-dioxo-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10H-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide.



Step 1. Preparation of **5-1:** HATU (555 mg, 1.46 mmol, Oakwood) and DIPEA (1.10 mL, 6.35 mmol) were added to a mixture of **1-2** (533 mg, 1.20 mmol) and Intermediate **D5** (414 mg, 1.33 mmol) in 12 mL of DMF under argon. After stirring overnight, the reaction mixture was poured into water and extracted three times with ethyl acetate. Combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0-35% ethyl acetate in hexanes) to yield **5-1** (713 mg) as a white solid. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{37}H_{54}ClN_4O_7$: 701.36; found: 701.58.

Step 2. Preparation of **5-2:** $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (94 mg, 0.115 mmol, Strem) was added to a deoxygenated mixture of **5-1** (710 mg, 1.01 mmol), potassium vinyltrifluoroborate (213 mg, 1.59 mmol), and triethylamine (0.210 mL, 1.52 mmol) in 11 mL of EtOH at room temperature. Reaction mixture was heated at 78 °C under argon for one hour. After cooling to room temperature, reaction mixture was poured into water and extracted three times with ethyl acetate. Combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield **5-2** (699 mg), which was used in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{39}H_{57}N_4O_7$: 693.41; found: 693.47.

Step 3. Preparation of **5-3:** A mixture of **5-2** (699 mg, 1.01 mmol) and Zhan 1 B catalyst (81 mg, 0.111 mmol, Strem) in 200 mL of DCE was deoxygenated under argon for 25 minutes. The mixture was then heated at 95 °C for 45 minutes. Reaction mixture was heated at 95 °C for 10 additional minutes, was cooled to room temperature, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0-30% ethyl acetate in hexanes) to yield **5-3** (336 mg) as a light brown solid. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{37}H_{53}N_4O_7$: 665.38; found: 665.53.

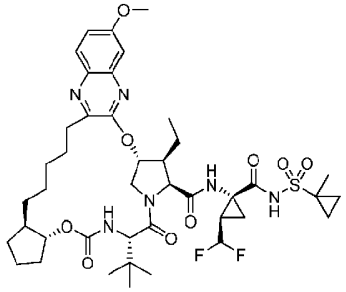
Step 4. Preparation of **5-4:** Palladium on carbon (10 wt. % Pd, 102 mg, 0.096 mmol) was added to a solution of **5-3** (330 mg,

0.497 mmol) in 8 mL of ethanol and 3.5 mL of ethyl acetate. Mixture was stirred under an atmosphere of hydrogen for 100 minutes and was then filtered over Celite, washing with ethyl acetate. Filtrate was concentrated under reduced pressure to yield **5-4** (64 mg) as a light yellow-brown solid film, which was used in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{37}H_{55}N_4O_7$: 667.40; found: 667.52.

Step 5. Preparation of **5-5:** TMSOTf (0.53 mL, 2.91 mmol) was added dropwise to a solution of **5-4** (329 mg, 0.494 mmol) in 10 mL of dichloromethane under argon at room temperature. After one hour, an additional 0.3 mL of TMSOTf was added. After an additional hour, reaction mixture was concentrated under reduced pressure. The resulting film was taken up in 12 mL of toluene and concentrated under reduced pressure. This process was repeated a second time to yield **5-5** (301 mg), which was used in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{47}N_4O_7$: 611.34; found: 611.46.

Step 6. Preparation of Example **5:** HATU (129 mg, 0.339 mmol) and DIPEA (0.22 mL, 1.27 mmol) were added to a mixture of **5-5** (134 mg, 0.22 mmol) and Intermediate **A9** (95 mg, 0.328 mmol) in 6.6 mL of MeCN under argon. After stirring for 5 h, reaction mixture was poured into water and extracted three times with ethyl acetate. Combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by reverse phase preparatory HPLC (15-100% acetonitrile in water, with 0.1% trifluoroacetic acid buffer) to yield Example **5** (43 mg) as a light yellow solid, trifluoroacetic acid salt, after lyophilization. Analytic HPLC RetTime: 9.11 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{41}H_{57}F_2N_6O_9S$: 847.38; found: 847.62. ^{1}H NMR (400 MHz, CD_3OD): δ 9.31 (s, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.23 (dd, J = 15.4, 2.8 Hz, 1H), 7.19 (d, J = 2.8 Hz, 1H), 5.87 (td, J_{H-F} = 56 Hz, J = 6 Hz, 1H), 5.87-5.83 (m, 1H), 4.59 (d, J = 7.6 Hz, 1H), 4.38 (s, 1H), 4.23-4.14 (m, 2H), 3.93 (s, 3H), 3.06-2.94 (m, 2H), 2.77-2.67 (m, 1H), 2.65-2.58 (m, 1H), 2.07-2.01 (m, 2H), 1.98-1.74 (m, 4H), 1.72-1.52 (m, 4H), 1.50-1.20 (m, 12H), 1.18-1.02 (m, 8H), 1.06 (s, 9H).

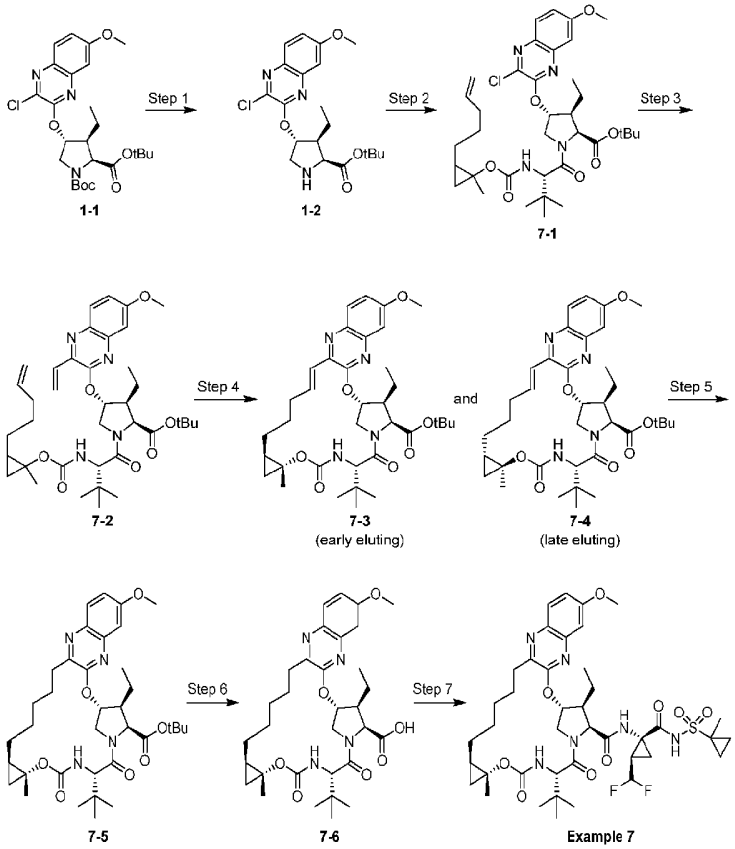
[0189] Example **6.** Preparation of (3aR,7S,10S,11S,12R,24aR)-7-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-11-ethyl-16-methoxy-5,8-dioxo-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10h-9,12-methanocyclopenta[18,19][1,10,3,6] dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide.



Example 6

[0190] Example **6** was prepared in a similar fashion to Example **5,** substituting Intermediate **A10** for Intermediate A9 in Step 6. Example **6** was isolated (29 mg) as a white solid. Analytic HPLC RetTime: 9.26 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{42}H_{59}F_2N_6O_9S$: 861.40; found: 861.20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.82 (d, J = 12Hz, 1H), 7.18 (d, J = 12 Hz 1H), 7.13-7.06 (m, 1H), 6.48 (s, 1 H), 5.95 (td, J_{H-F} = 56 Hz, J = 6 Hz, 1 H), 5.82 (d, J = 4.4 Hz, 1 H), 5.33 (d, J = 10 Hz, 1 H), 4.95-4.91 (m, 1 H), 4.38-4.31 (m, 2H), 4.10-3.88 (m, 2H), 3.98 (s, 3H), 2.98-2.89 (m, 1 H), 2.67-2.59 (m, 1 H), 2.05-1.65 (m, 4H), 1.64-1.21 (m, 12H), 1.40 (s, 3H), 1.17-0.80 (m, 12H), 1.09 (s, 9H).

[0191] Example **7.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1 R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-14-methoxy-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6] dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Step 1. Preparation of **1-2** (free base): Carbamate **1-1** (350 mg, 0.689 mmol) was added to a flask containing a 4:1 mixture of t-butyl acetate:DCM (3.5 mL). To this solution was then added methanesulfonic acid (447 µL, 6.89 mmol). The reaction mixture was allowed to stir for 20 min at rt, then diluted with methylene chloride (20 mL) and saturated aqueous sodium bicarbonate (20 mL). The solution was allowed to stir until evolution of gas ceased, then the organics were removed and the aqueous layer was extracted twice with methylene chloride (20 mL). The combined organics were then washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting white solid **1-2** (free base, 280 mg) was used in the subsequent reaction without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{20}H_{27}ClN_3O_4$: 408.2; found: 408.1

Step 2. Preparation of mixture **7-1:** Amine **1-2** (281 mg, 0.689 mmol) was combined with diastereomeric Intermediate mixture **D6** (266 mg, 0.895 mmol), DIPEA (600 µL, 3.45 mmol) and DMF (2 mL). HATU (340 mg, 0.895 mmol) was then added to the reaction mixture, which was stirred at 40 °C for 5 h. Reaction mixture was then diluted with water (10 mL) and taken up into methylene chloride (10 mL). Organics were separated and aqueous layer was extracted once with methylene chloride (10 mL). Combined organics were then washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Crude residue was then purified via silica gel chromatography to give **7-1** as a 1:1 diastereomeric mixture (280 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{36}H_{52}ClN_4O_7$: 687.4; found: 687.3.

Step 3. Preparation of **7-2:** $Pd(dppf)Cl_2$ (29 mg, 0.0407 mmol) was added to a degassed mixture of **7-1** (280 mg, 0.407 mmol), potassium vinyltrifluoroborate (55 mg, 0.733 mmol), and triethylamine (91 µL, 0.651 mmol) in 2 mL of ethanol at room temperature. Reaction mixture was heated at 80 °C under N_2 for one hour. After cooling to room temperature, reaction mixture was diluted with toluene (10 mL), concentrated *in vacuo* to a small volume of solvent, and rediluted in toluene (1 mL). Mixture was then loaded directly onto a silica column and purified by silica gel chromatography to afford **7-2** as a 1:1 diastereomeric mixture which was carried on to the next step without concentrating fully to dryness. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{38}H_{55}N_4O_7$: 679.4; found: 679.4.

Step 4. Preparation of **7-3** and **7-4:** Diastereomeric mixture **7-2** (276 mg, 0.407 mmol) and Zhan 1 B catalyst (32 mg, 0.0407 mmol, Strem) were dissolved in 80 mL of DCE and degassed under N_2 for 25 minutes. The mixture was then heated to 100 °C for 1 h. Reaction was then cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified via silica gel chromatography (0% to 30% ethyl acetate in hexanes) to yield single diastereomers **7-3** (20 mg, early eluting fraction) and **7-4** (25 mg, late eluting fraction) as light brown residues. Early eluting fraction: LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{51}N_4O_7$:

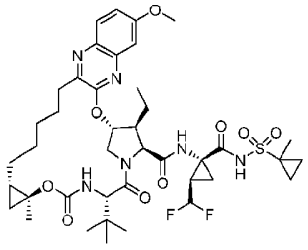
651.4; found: 651.3. Late eluting fraction: LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{36}H_{51}N_4O_7$: 651.4; found: 651.3.

Step 5. Preparation of **7-5:** Palladium on carbon (10% w/w, 25 mg) was added to a solution of **7-3** (20 mg, 0.0307 mmol) in a 1:1 mixture of ethyl acetate and dioxane (2 mL). Mixture was stirred under an atmosphere of hydrogen for 30 min and was then filtered through a plug of Celite, and washed with ethyl acetate. Filtrate was concentrated under reduced pressure to yield **7-5** (16 mg) as a light brown film, which was used in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{53}N_4O_7$: 653.4; found: 653.4.

Step 6. Preparation of **7-6:** Intermediate **7-5** (16 mg, 0.023 mmol) was dissolved in 2 M HCl in dioxane (2 mL) and heated at 80 °C for 1.5 h via microwave reactor. Reaction mixture was then concentrated *in vacuo* to give **7-6** (15 mg) as a brown residue, which was used in the subsequent step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{44}N_4O_7$: 597.3; found: 597.3.

Step 7. Preparation of Example **7:** HATU (11.9 mg, 0.031 mmol) and DIPEA (22 µL, 0.126 mmol) were added to a mixture of **7-6** (15 mg, 0.025 mmol) and **A10** (11.5 mg, 0.0377 mmol) in 1 mL of DMF. After stirring overnight at room temperature, reaction mixture was poured into water, acidified to pH 1 with 1N aqueous HCl, and extracted three times with methylene chloride (15 mL). Combined organics were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by reverse phase prep HPLC (5-100% acetonitrile in water, with 0.1% trifluoroacetic acid buffer) followed by silica gel chromatography to afford Example 7 (4.3 mg) as a white solid film. Analytic HPLC RetTime: 9.07 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{41}H_{57}F_2N_6O_9S$: 847.4; found: 847.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.83 (d, J = 9.1 Hz, 1H), 7.20 (dd, J = 9.1 Hz, 2.8 Hz, 1H), 7.07 (d, J = 2.7 Hz, 1H), 6.56 (s, 1H), 5.98 (td, J_{H-F} = 55.7, J = 6.7 Hz, 1H), 5.95 (d, J = 9.6, 1 H), 5.32 (d, J = 9.6 Hz, 1H), 4.45 (dd, J = 13.0 Hz, 9.6 Hz, 2H), 4.32 (d, J = 9.7 Hz, 1 H), 4.13 (dd, J = 15.5 Hz, 8.8 Hz, 1H), 3.93 (s, 3H), 2.99 - 2.84 (m, 1H), 2.82 - 2.68 (m, 1H), 2.62 - 2.47 (m 1H), 2.16 - 2.02 (m, 1H) 2.00-1.85 (m, 1H) 1.84-1.69 (m, 1H), 1.70 - 1.15 (m, 11H), 1.52 (s, 3H), 1.50 (s, 3H), 1.20 (t, J = 7.3 Hz, 3H), 1.14 - 0.77 (m, 5H) 1.09 (s, 9H), 0.11 (m, 1H).

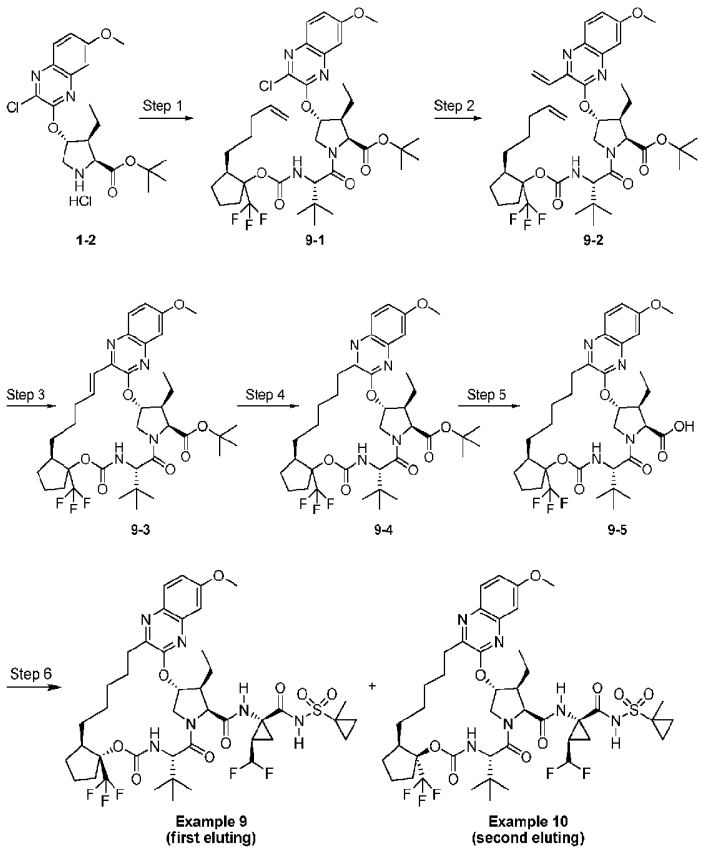
[0192] Example **8.** Preparation of (1aS,5S,8S,9S,10R,22aS)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-14-methoxy-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6] dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 8

[0193] Example **8** was prepared in a similar fashion to Example **7,** substituting late eluting **7-4** for early eluting **7-3** in Step 5. Example **7** was isolated (2.9 mg) as a white solid. Analytic HPLC RetTime: 9.09 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{41}H_{57}F_2N_6O_9S$: 847.4; found: 847.4.

[0194] Examples **9** and **10.** Preparation of (7S,10S,11S,12R)-7-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl} cyclopropyl]-11-ethyl-16-methoxy-5,8-dioxo-3aR-(trifluoromethyl)-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10H-9,12-methanocyclopenta[18,19] [1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide and (7S,10S,11S,12R)-7-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-11-ethyl-16-methoxy-5,8-dioxo-3aS-(trifluoromethyl)-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10H-9,12-methanocyclopenta[18,19][1,10,3,6] dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide.



Step 1. Preparation of **9-1:** To a solution of Intermediate **D8** (322 mg, 0.85 mmol) and **1-2** (316 mg, 0.78 mmol) in MeCN (3.9 mL) was added HATU (323 mg, 0.85 mmol) followed by DIPEA (678 µL, 3.90 mmol) at rt under an argon atmosphere. After 2 h, the reaction mixture was concentrated *in vacuo,* and the crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford amide **9-1** (476 mg, 1:1 diastereomeric mixture) as a colorless oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{38}H_{53}ClF_3N_4O_7$: 769.4; found: 769.5.

Step 2. Preparation of **9-2:** To a solution of **9-1** (470 mg, 612 µmol), TEA (128 µL, 918 µmol), and potassium vinyltrifluoroborate (123 mg, 918 µmol) in EtOH (3.06 mL) was added PdCl2(dppf) (50 mg, 61 µmol). The reaction mixture was deoxygenated with argon for 10 min and heated to 78 °C. After 1 h, the reaction mixture was allowed to cool to rt and was concentrated in vacuo. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford vinyl quinoxaline **9-2** (329 mg, 1:1 diastereomeric mixture) as a yellow oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{40}H_{56}F_3N_4O_7$: 761.4; found: 761.6.

Step 3. Preparation of **9-3:** To a solution of **9-2** (329 mg, 485 µmol) in DCE (97 mL) was added Zhan 1B catalyst (35 mg, 49 µmol, Strem) and the reaction mixture was deoxygenated for 10 minutes with argon. The reaction mixture was then heated to 100 °C. After 30 min, the reaction mixture was allowed to cool to rt and was concentrated *in vacuo.* The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford macrocycle **9-3** (301 mg, 7:4 diastereomeric mixtures) as a light yellow oil. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{38}H_{52}F_3N_4O_7$: 733.4; found: 733.5.

Step 4. Preparation of **9-4:** To a solution of **9-3** (300 mg, 410 µmol) in ethanol (2.00 mL) was added Pd/C (10 wt % Pd, 43 mg, 41 µmol) at rt under an argon atmosphere. The atmosphere of the reaction was replaced with hydrogen gas and the reaction mixture stirred vigorously at rt. After 30 min, the reaction mixture was diluted with ethyl acetate (10 mL) and filtered through a pad of Celite with ethyl acetate washings (3 × 5 mL). The filtrate was concentrated *in vacuo* to afford macrocycle **9-4** (295 mg, 7:4 diastereomeric mixture), which was used directly in the next step without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{38}H_{54}F_3N_4O_7$: 735.4; found: 735.5.

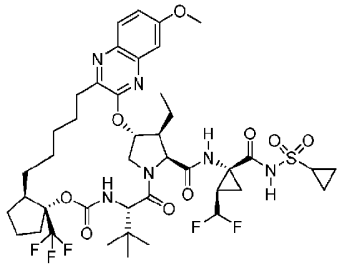
Step 5. Preparation of **9-5:** To a solution of **9-4** (295 mg, 401 µmol) in DCM (2 mL) was added TMSOTf (72.6 µL, 401 mmol) at rt under an argon atmosphere. After 1.5 h, additional TMSOTf (362.9 µL, 2.00 mmol) was added. After 1 h, additional TMSOTf (362.9 µL, 2.00 mmol) was added. After 2 h, the reaction mixture was added slowly to a 0.25 N aqueous NaOH solution (precooled to 0 °C, 3 mL). The resulting mixture was diluted with 1 N aqueous HCl solution (5 mL), and was extracted with DCM (3 × 5 mL).

The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated to afford carboxylic acid **9-5** (353 mg, 7:4 diastereomeric mixture) as a tan solid, which was used directly in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{45}F_3N_4O_7$: 679.3; found: 679.5.

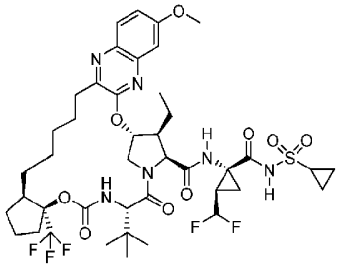
Step 6. Preparation of Example **9** and Example **10:** To a solution of acid **9-5** (150 mg, 220 µmol) and Intermediate **A10** (101 mg, 330 µmol) in MeCN (1.1 mL) was added HATU (127 mg, 330 µmol) followed by DIPEA (191 µL, 1.10 mmol) at rt under an argon atmosphere. After 1 h, the reaction mixture was concentrated *in vacuo,* and the crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient). The fractions containing the desired product were combined and were repurified by silica gel chromatography (0-50% acetone/hexanes gradient) to afford the first eluting

[0195] Example **9** (40 mg) as a white powder and the second eluting Example **10** (70 mg) as a white powder. First eluting Example **9:** Analytic HPLC RetTime: 9.42 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{43}H_{58}F_5N_6O_9S$: 929.4; found: 929.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.92 (d, *J* = 9.1 Hz, 1H), 7.19 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.13 (d, *J* = 2.6 Hz, 1H), 5.99 (br s, 1H), 5.96 (td, J_{H-F} 55.5, *J* = 6.6 Hz, 1H), 5.70 (d, *J* = 10.0 Hz, 1H), 4.63 (d, *J* = 6.6 Hz, 1H), 4.38 (d, *J* = 10.0 Hz, 1H), 4.22 - 4.04 (m, 2H), 3.96 (s, 3H), 3.12 - 2.89 (m, 1H), 2.71 - 2.51 (m, 2H), 2.17 (s, 3H), 2.15 - 1.82 (m, 4H), 1.83 - 1.34 (m, 8H), 1.36 - 0.98 (m, 12H), 1.26 (s, 9H), 0.92 - 0.79 (m, 4H). Second eluting Example **10:** Analytic HPLC RetTime: 9.55 min. LCMS-ESI$^+$ *(m/z):* $[M+H]^+$calcd for $C_{43}H_{58}F_5N_6O_9S$: 929.4; found: 929.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.91 (d, *J* = 9.1 Hz, 1H), 7.23 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.18 (d, *J* = 2.7 Hz, 1H), 5.98 - 5.91 (m, 1H), 5.83 (td, J_{H-F} 55.5, *J* = 6.6 Hz, 1H), 5.33 (d, *J* = 9.8 Hz, 1H), 4.72 - 4.63 (m, 1H), 4.46 - 4.38 (m, 1 H), 4.32 (d, *J* = 10.0 Hz, 1H), 4.25 - 4.14 (m, 1H), 3.97 (s, 3H), 3.73 (br d, *J* = 7.6 Hz, 1H), 3.23 - 3.07 (m, 1H), 2.86 - 2.37 (m, 2H), 2.14 - 1.79 (m, 2H), 1.78 - 1.38 (m, 8H), 1.51 (s, 3H), 1.35 - 1.08 (m, 8H), 1.25 (s, 9H), 1.05 (br s, 3H), 0.93 - 0.68 (m, 6H).

[0196] Examples **11** and **12.** Preparation of (7S,10S,11S,12R)-7-tert-butyl-N-[(1 R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-11-ethyl-16-methoxy-5,8-dioxo-3aR-(trifluoromethyl)-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10H-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide and (7S,10S,11S,12R)-7-tert-butyl-N-[(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-11-ethyl-16-methoxy-5,8-dioxo-3aS-(trifluoromethyl)-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10H-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide.



Example 11
(first eluting)

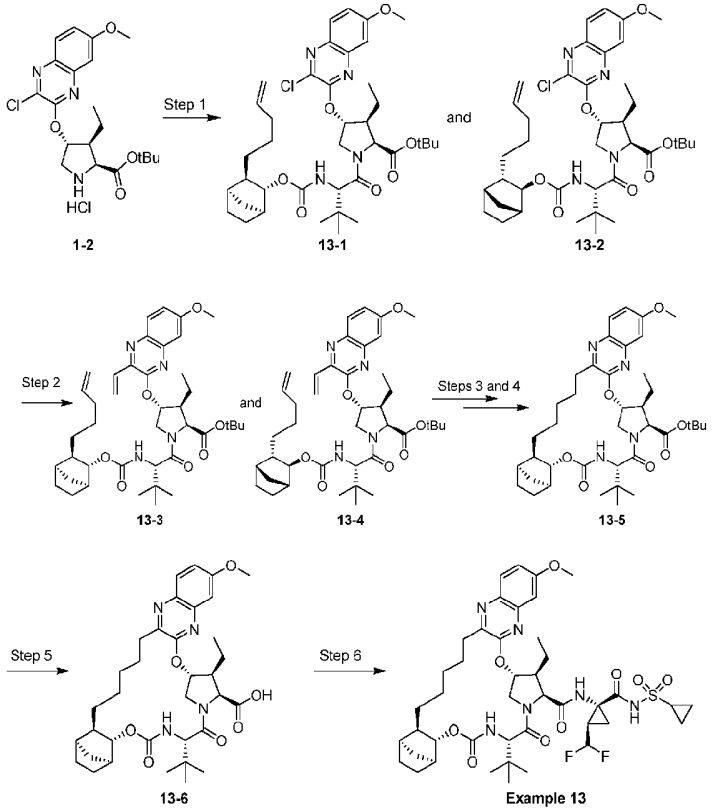


Example 12
(second eluting)

[0197] Preparation of Example **11** and Example **12:** To a solution of acid **9-5** (150 mg, 220 µmol) and Intermediate **A9** (96 mg, 330 µmol) in MeCN (1.1 mL) was added HATU (127 mg, 330 µmol) followed by DIPEA (191 µL, 1.10 mmol) at rt under an argon atmosphere. After 1 h, the reaction mixture was concentrated *in vacuo,* and the crude residue was purified by silica gel chromatography (0-50% acetone/hexanes gradient). The fractions containing the desired product were combined and were repurified by silica gel chromatography (0-50% acetone/hexanes gradient) to afford the first eluting Example **11** (29 mg) as a white powder and the second eluting Example **12** (60.2 mg) as a white powder. First eluting Example **11:** Analytic HPLC RetTime: 9.44 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd $C_{42}H_{56}F_5N_6O_9S$: 915.4; found: 915.6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (br s, 1H), 7.83 (d, *J* = 9.1 Hz, 1H), 7.21 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.17 - 7.07 (m, 1H), 5.99 (br s, 1H), 5.97 (td, J_{H-F} 55.5, *J* = 6.6 Hz, 1H), 5.82 (d, *J* = 9.8 Hz, 1H), 4.55 (d, *J* = 7.2 Hz, 1H), 4.39 (d, *J* = 10.0 Hz, 1H), 4.20 - 4.03 (m, 2H), 3.95 (s, *J* = 5.9 Hz, 3H), 2.97 - 2.82 (m, 2H), 2.79 - 2.49 (m, 3H), 2.24 - 1.81 (m, 8H), 1.80 - 1.11 (m, 12H), 1.10 - 0.98 (m, 4H), 1.07 (s, 9H), 0.95 - 0.81 (m, 3H). Second eluting Example **12:** Analytic HPLC RetTime: 9.48 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd $C_{42}H_{56}F_5N_6O_9S$: 915.4; found: 915.6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.93 (d, *J* = 9.6 Hz, 1H), 7.28 - 7.20 (m, 1H), 7.16 (s, 1H), 6.17 - 5.68 (m, 3H), 4.67 - 4.55 (m, 1 H), 4.37 - 4.23 (m, 2H), 4.17 - 4.05 (m, 1H), 3.97 (s, 3H), 3.75 - 3.66 (m, 1H), 3.22 - 3.04 (m, 1H), 3.02 - 2.31 (m,

6H), 2.30 - 1.83 (m, 10H), 1.85 - 1.13 (m, 13H), 1.06 (s, 9H), 0.95 - 0.79 (m, 1 H).

[0198] Example **13**. Preparation of (1R,4S,4aR,8S,11S,12S,13R,25aR)-8-tert-butyl-N-[(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-12-ethyl-17-methoxy-6,9-dioxo-2,3,4,4a,6,7,8,9,12,13,21,22,23,24,25,25a-hexadecahydro-1H,11H-1,4:10,13-dimethanoquinoxalino[2,3-k][1,10,3,6]benzodioxadiazacyclononadecine-11-carboxamide.



Step 1. Preparation of diastereomer mixture **13-1** and **13-2:** To a solution of **1-2** (354 mg, 0.87 mmol), Intermediate mixture **D9** and **D10** (323 mg, 0.96 mmol) and BEP (263 mg, 0.96 mmol; TCI America) was added DIPEA (0.45 mL, 2.61 mmol) and the reaction was stirred at 50 °C for 2 h. The reaction was quenched with sat. aqueous $NaHCO_3$ solution and extracted with EtOAc, the organic phase was washed with brine, dried over magnesium sulfate and concentrated. The crude product was purified by silica gel chromatography (0-30% EtOAc/hexanes) to yield an inseparable mixture of diastereomers **13-1** and **13-2** (338 mg). LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{39}H_{56}ClN_4O_7$: 727.38; found: 727.46.

Step 2. Preparation of diastereomer mixture **13-3** and **13-4:** To a solution of the mixture of **13-1** and **13-2** (338 mg, 0.46 mmol), TEA (0.10 mL, 0.69 mmol) and potassium vinyltrifluoroborate (93 mg, 0.69 mmol) in EtOH (30 mL) was added $PdCl_2$(dppf) (38 mg, 0.046 mmol, Strem Chemicals). The reaction was deoxygenated with N_2 for 10 min and heated to 80 °C for 1 h. The reaction was quenched with sat. aqueous $NaHCO_3$ solution and extracted with EtOAc, washed subsequently with brine, dried over magnesium sulfate and concentrated. The residue was purified using silica gel chromatography to give an inseparable mixture of diastereomers **13-3** and **13-4** (285 mg). LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{41}H_{59}N_4O_7$: 719.44; found: 719.70.

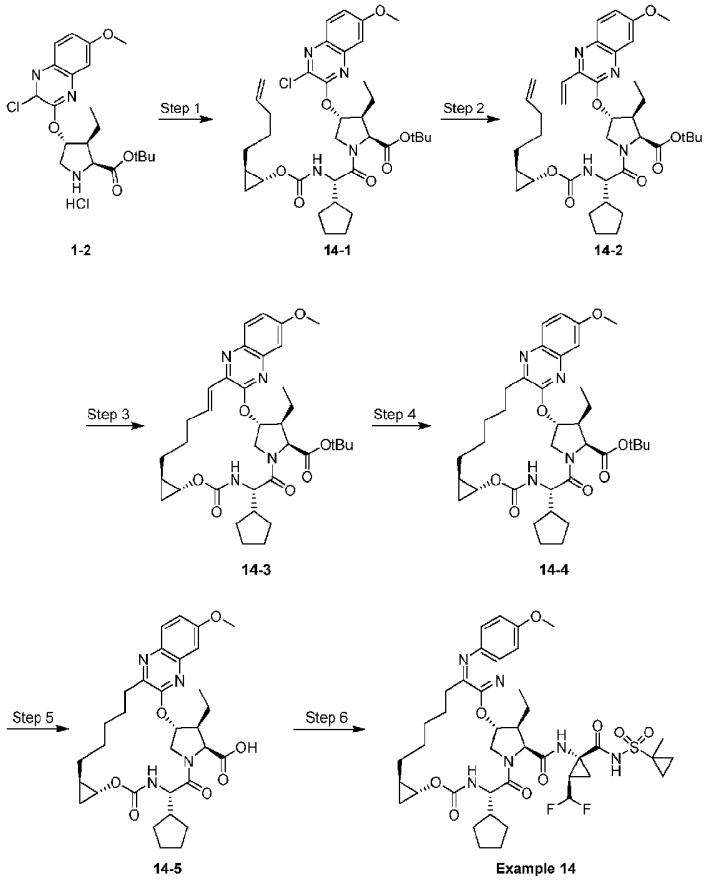
Step 3 and 4. Preparation of **13-5:** To a solution of the diastereomeric mixture **13-3** and **13-4** (285 mg, 0.40 mmol) in DCE (100 mL) was added Zhan 1B catalyst (30 mg, 0.04 mmol, Strem) and the reaction was deoxygenated for 30 minutes with N_2. The reaction was heated to 100 °C for 45 min, allowed to cool to rt and concentrated. The crude product was purified by silica gel chromatography to produce macrocyclic olefin product (125 mg; LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{39}H_{55}N_4O_7$: 691.41; found: 691.58) that was taken up in EtOH (6 mL) and treated with Pd/C (10%, 120 mg). The atmosphere was replaced with hydrogen and stirred at rt for 1.5 h. The reaction was filtered over Celite, washed with EtOAc and concentrated to give **13-5** as an oil (125 mg) that was used subsequently without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{39}H_{57}N_4O_7$: 693.42; found: 693.46.

Step 5. Preparation of **13-6:** To a solution of **13-5** (50 mg, 0.072 mmol) in DCM (4 mL) was added TFA (1 mL) and stirred at rt for

6 h. The reaction was diluted with EtOAc, washed with H_2O, aqueous pH 7 buffer, dried over magnesium sulfate, and concentrated to give **13-6** as a residue that was used subsequently without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{35}H_{49}N_4O_7$: 637.36; found: 637.40.

Step 6. Preparation of Example **13:** To a solution of **13-6** (46 mg, 0.072 mmol), Intermediate **A9** (28 mg, 0.11 mmol), TBTU (34 mg, 0.10 mmol) and DMAP (13 mg, 0.11 mmol) in DCM (5 mL) was added DIPEA (0.038 mL, 0.22 mmol) and the reaction was stirred at rt for 16 h. The reaction was quenched with water, diluted with EtOAc, washed with sat. aqueous $NaHCO_3$, brine, dried over magnesium sulfate, and concentrated. The crude material was purified by reverse phase HPLC (Gemini, 30-85% MeCN/H_2O + 0.1% TFA) and lyophilized to give Example **13** (14.5 mg) as a TFA salt. Analytic HPLC RetTime: 9.39 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{43}H_{59}F_2N_6O_9S$: 873.40; found: 873.42. ^1H NMR (400 MHz, CD_3OD) δ 9.28 (s, 1H), 7.82 (d, J = 9.2 Hz, 1H), 7.26 (dd, J = 6.4, 2.8 Hz, 1H), 7.19 (d, J = 2.8 Hz, 1H), 6.04 - 5.74 (m, 2H), 5.50 (s, 1H), 4.55 (d, J = 7.6 Hz, 1H), 4.47 (s, 1 H), 4.26 - 4.16 (m, 2H), 3.94 (s, 3H), 3.03 - 2.95 (m, 2H), 2.78 - 2.66 (m, 2H), 2.17 (br, 2H), 2.05 (s, 3H), 1.90 - 1.85 (m, 1H), 1.76 - 1.74 (m, 2H), 1.61 - 1.21 (m, 20H), 1.15 - 1.11 (m, 2H), 1.08 (s, 9H), 0.93 - 0.90 (m, 1 H).

[0199] Example **14.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-cyclopentyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Step 1. Preparation of **14-1:** To a solution of **1-2** (223 mg, 0.50 mmol) and Intermediate **D2** (221 mg, 0.75 mmol) in acetonitrile (5 mL) was added HATU (306 mg, 0.80 mmol) followed by DIPEA (0.43 mL, 2.5 mmol) at room temperature. After 19 h, solvent was removed under reduced pressure and the resulting residue was diluted with ethyl acetate (15 mL). The resulting solution was washed with 1 M aqueous HCl (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL) and combined organic layer was washed with brine (15 mL), dried over anhydrous magnesium sulfate and concentrated. The resulting crude residue was purified via silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford **14-1** (173 mg) as colorless oil. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{36}H_{50}ClN_4O_7$: 685.33; found: 685.49.

Step 2. Preparation of **14-2:** To a solution of **14-1** (173 mg, 0.25 mmol) in EtOH (3 mL) was added potassium vinyltrifluoroborate

(51 mg, 0.38 mmol), $PdCl_2$(dppf) (21 mg, 0.025 mmol) and TEA (0.053 mL, 0.38 mmol) sequentially and the resulting mixture was heated to 80 °C. After 1 h, additional potassium vinyltrifluoroborate (17 mg, 0.12 mmol) was added and continued stirring at 80 °C. After 2.5 h, additional potassium vinyltrifluoroborate (8 mg, 0.06 mmol) was added and the reaction was stirred for additional 10 minutes at 80 °C. The reaction was cooled to room temperature, diluted with ethyl acetate (20 mL), and washed with brine (20 mL). Aqueous layer was extracted with ethyl acetate (10 mL), and the combined organic layer was dried over anhydrous magnesium sulfate and concentrated to afford **14-2** as a residue which was used it without purification in the next step. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{38}H_{53}N_4O_7$: 677.38; found: 677.50.

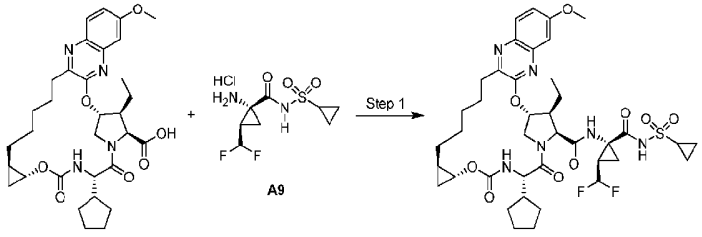
Step 3. Preparation of **14-3:** To a solution of **14-2** in deoxygenated DCE (0.006 M) was added Zhan 1B catalyst (18 mg, 0.025 mmol, Strem) and the reaction was deoxygenated for another 10 minutes with Ar. The reaction was heated to 100 °C. After 1.5 h, Zhan 1B catalyst (9 mg, 0.012 mmol) was added and the reaction was stirred for another 30 min. The reaction mixture was allowed to cool to rt and concentrated to 4-5 mL volume. This was directly purified by silica gel chromatography to afford **14-3** as a brown oil (70 mg). LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{36}H_{49}N_4O_7$: 649.35; found: 649.50.

Step 4. Preparation of **14-4:** To a solution of **14-3** (70 mg, 0.11 mmol) in EtOH (5 mL) was added Pd/C (10 wt % Pd, 12 mg) under argon. The atmosphere was replaced with hydrogen and the reaction was stirred at rt for 16 h. The reaction was filtered over Celite, washed with EtOH and concentrated to give **14-4** as a brown oil that was used subsequently without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{51}N_4O_7$: 651.37; found: 651.60.

Step 5. Preparation of **14-5:** To a solution of **14-4** (70 mg, 0.11 mmol) in DCM (3 mL) was added TMSOTf (0.103 mL, 0.53 mmol) and the reaction was stirred at rt for 1 h. The reaction was concentrated to afford **14-5** which was used it for the next step without purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{43}N_4O_7$: 595.31; found: 595.43.

Step 6. Preparation of Example **14:** To a solution of **14-5** (36.8 mg, 0.06 mmol) and Intermediate **A10** (28 mg, 0.09 mmol) in acetonitrile (1.5 mL) was added HATU (38 mg, 0.1 mmol) followed by DIPEA (0.065 mL, 0.37 mmol) at room temperature. After 20 minutes, the reaction mixture was directly purified by reverse phase HPLC (Gemini 5u C18 110A column, 15-100% MeCN/H_2O + 0.1% TFA) and lyophilized to afford Example **14** as a yellow solid (24 mg) as a TFA salt. Analytic HPLC RetTime: 9.03 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{41}H_{55}F_2N_6O_9S$: 845.4; found: 845.6. ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (s, 1H), 7.80 (d, *J* = 9.1 Hz, 1H), 7.23 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.16 (d, *J* = 2.7 Hz, 1H), 6.03 - 5.66 (m, 2H), 4.53 (dd, *J* = 13.2, 9.6 Hz, 2H), 4.18 (dd, *J* = 17.2, 7.1 Hz, 2H), 3.92 (s, 3H), 3.68 (dt, *J* = 6.8, 2.8 Hz, 1 H), 3.13 (quin, *J* = 1.7 Hz, 1H), 3.02 - 2.92 (m, 1H), 2.85 - 2.78 (m, 1H), 2.62 - 2.55 (m, 1 H), 2.30 - 2.17 (m, 1H), 2.02 (s, 2H), 1.97 - 1.86 (m, 3H), 1.86 - 1.79 (m, 1H), 1.80 - 1.41 (m, 17H), 1.40 - 1.28 (m, 3H), 1.22 (t, *J* = 7.4 Hz, 3H), 1.03 - 0.87 (m, 4H), 0.76 - 0.68 (m, 1H), 0.51 - 0.44 (m, 1 H).

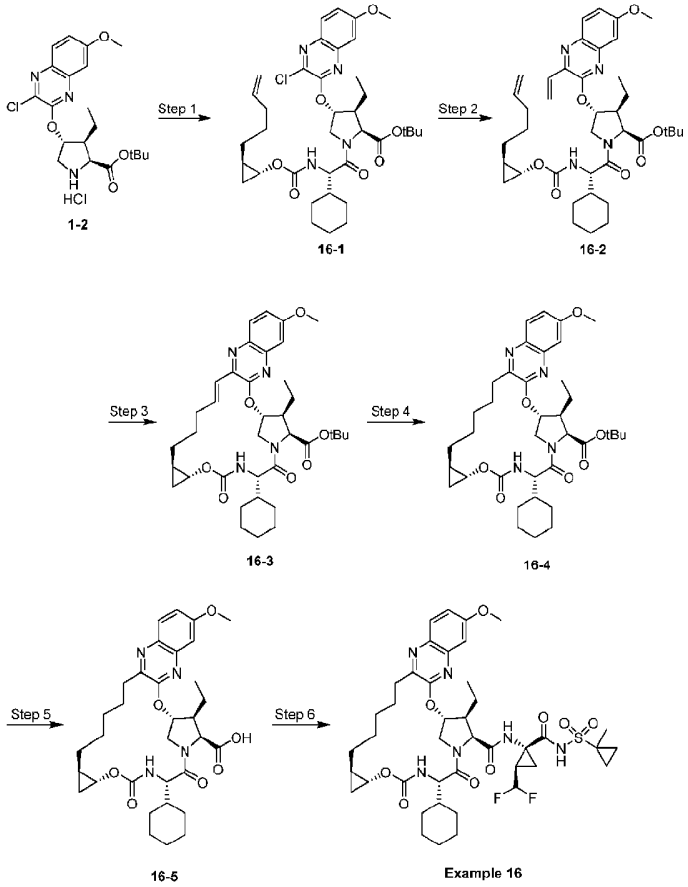
[0200] Example **15.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-cyclopentyl-N-[(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-9-ethyl-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



[0201] Step 1. Preparation of Example **15.** To a solution of **14-5** (27 mg, 0.045 mmol) and Intermediate **A9** (20 mg, 0.067 mmol) in acetonitrile (1.3 mL) was added HATU (27 mg, 0.072 mmol) followed by DIPEA (0.047 mL, 0.27 mmol) at room temperature. After 20 minutes, the reaction mixture was directly purified by reverse phase HPLC (Gemini 5u C18 110A column, 15-100% MeCN/H_2O + 0.1% TFA) and lyophilized to afford Example **15** as a yellow solid (18.6 mg) as a TFA salt. Analytic HPLC RetTime: 8.89 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{40}H_{53}F_2N_6O_9S$: 831.4; found: 831.6. ^{1}H NMR (400 MHz, CD_3OD) δ 9.32 (s, 1H), 7.79 (d, *J* = 9.1 Hz, 1H), 7.23 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.16 (d, *J* = 2.8 Hz, 1H), 6.03 - 5.66 (m, 2H), 4.53 (t, *J* = 10.0 Hz, 2H), 4.22 - 4.14 (m, 2H), 3.92 (s, 3H), 3.67 (dt, *J* = 6.5, 2.9 Hz, 1H), 3.13 (quin, 1.6 Hz, 1H), 3.04 - 2.92 (m, 3H), 2.85 - 2.77 (m, 1H), 2.63 - 2.55 (m, 1H), 2.26 - 2.19 (m, 1H), 2.05 - 2.02 (m, 2H), 1.99 - 1.86 (m, 3H), 1.84 - 1.42 (m, 12H), 1.41 - 1.25 (m, 4H), 1.22 (t, *J* =

7.2 Hz, 3H), 1.15 - 1.03 (m, 3H), 1.01 - 0.90 (m, 2H), 0.76 - 0.68 (m, 1H), 0.49 - 0.45 (m, 1H).

[0202] Example **16.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-cyclohexyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Step 1. Preparation of **16-1:** To a solution of Intermediate **D3** (190 mg, 0.60 mmol) and **1-2** (264 mg, 0.60 mmol) in DMF (5 mL) was added DIPEA (0.31 mL, 1.8 mmol) followed by COMU (257 mg, 0.60 mmol) at rt. After 2 h, the solvent was removed under reduced pressure and the resulting residue diluted with ethyl acetate (15 mL). The resulting solution was washed with 10% aqueous citric acid solution. The aqueous layer was extracted with ethyl acetate (2 × 10 mL) and combined organic layer was washed with brine (15 mL), dried over anhydrous magnesium sulfate and concentrated. The resulting crude residue was purified via silica gel chromatography to afford **16-1** (260 mg) as a colorless oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{37}H_{51}ClN_4O_7$: 700.28; found: 700.03.

Step 2. Preparation of **16-2:** To a solution of **16-1** (260 mg, 0.37 mmol) in EtOH (5 mL) were added potassium vinyltrifluoroborate (75 mg, 0.56 mmol), $PdCl_2$(dppf) (30 mg, 0.037 mmol) and TEA (0.079 mL, 0.56 mmol) sequentially. The reaction was deoxygenated with Ar for 12 min and was heated to 78 °C for 2 h. The reaction was cooled to rt, diluted with ethyl acetate (20 mL), and washed with brine (20 mL). The aqueous layer was extracted with ethyl acetate (10 mL), and the combined organic layers were dried over anhydrous magnesium sulfate and concentrated to afford crude residue. The resulting crude residue was purified via silica gel chromatography to afford **16-2** as a yellow oil (250 mg). LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{39}H_{54}N_4O_7$: 691.87; found: 691.54.

Step 3. Preparation of **16-3:** To a solution of **16-2** (250 mg, 0.36 mmol) in deoxygenated DCE (0.005 M) was added Zhan 1B catalyst (26 mg, 0.036 mmol, Strem) and the reaction was deoxygenated for another 10 minutes with Ar. The reaction was heated to 70 °C for 2 h. The reaction mixture was allowed to cool to rt and concentrated. The resulting residue was directly purified by silica gel chromatography to afford **16-3** as a yellow oil (250 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{37}H_{50}N_4O_7$: 663.82; found: 663.42.

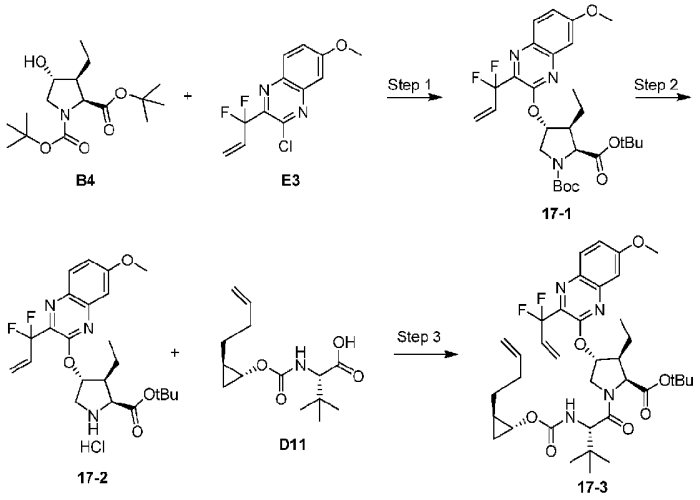
Step 4. Preparation of **16-4:** To a solution of **16-3** (200 mg, 0.3 mmol) in EtOAc (10 mL) was added Pd/C (10 wt % Pd, 100 mg)

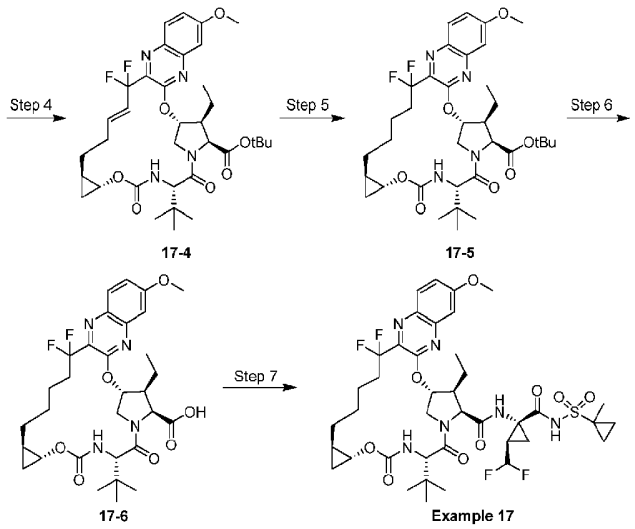
under argon. The atmosphere was replaced with hydrogen and the reaction was stirred at rt for 1.5 h. The reaction was filtered over Celite, washed with EtOH and concentrated to give **16-4** as an oil (180 mg) that was used subsequently without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{37}H_{52}N_4O_7$: 665.83; found: 665.36.

Step 5. Preparation of **16-5:** To a solution of **16-4** (165 mg, 0.25 mmol) in DCM (5 mL) was added TFA (2 mL) and the reaction was stirred at rt for 4 h. The solvent was removed under reduced pressure the reaction was diluted with ethyl acetate (15 mL). The resulting solution was washed with sat. aqueous $NaHCO_3$ and concentrated to afford **16-5** which was used in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{44}N_4O_7$: 609.73; found: 609.47

Step 6. Preparation of Example **16:** To a solution of **16-5** (70 mg, 0.12 mmol) and Intermediate **A10** (65 mg, 0.21 mmol) in DCM (1 mL) was added DIPEA (0.08 mL, 0.46 mmol) followed by HATU (88 mg, 0.23 mmol). The reaction was stirred at room temperature for 3 h. The reaction was diluted with EtOAc and washed with aqueous NH_4Cl and brine. The crude material was purified by reverse phase HPLC (Gemini column, 58-98 % MeCN/H_2O + 0.1% TFA) and lyophilized to afford Example **16** (40 mg) as a TFA salt. Analytic HPLC RetTime: 9.21 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{42}H_{56}F_2N_6O_9S$: 859.99; found: 859.60. ^1H NMR (400 MHz, CD_3OD) δ 9.28 (s, 1H), 7.76 (d, *J* = 9.2 Hz, 1H), 7.18 (d, *J* = 9.2 Hz, 1H), 7.10 (s, 1H), 5.97 - 5.82 (m, 2H), 4.88 (m, 2H), 4.51-4.46 (m, 3H), 4.19-4.11 (m, 3H), 3.90 (s, 3H), 3.70-3.29 (m, 6H), 2.97-2.52 (m, 3H), 2.06 - 1.41 (m, 20H), 1.39 - 1.17 (m, 4H), 1.09 - 0.89 (m, 4H), 0.65 (m, 1 H), 0.46 - 0.44 (m, 1H).

[0203] Example **17.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1 R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-18,18-difluoro-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.





Steps 1 and 2. Preparation of **17-2:** A mixture of Intermediate **B4** (273 mg, 0.865 mmol), Intermediate **E3** (234 mg, 0.865 mmol), and cesium carbonate (310 mg, 0.952 mmol) in MeCN (2.5 mL) was heated at 85 °C for 36 hours. In an alternative process, DMF was used as the solvent. Water (10 mL) was added and the mixture was extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and concentrated to afford **17-1,** which was used subsequently without further purification or after chromatography purification. The residue was treated with 35 equiv 4 N HCl in dioxane at rt for 2.5 hours. Upon addition of diethyl ether, the hydrochloride salt of **17-2** precipitated. The salt was collected by vacuum filtration and dried under reduced pressure (375 mg). In an alternative process, the deprotection was conducted in the presence of MSA in tBuOAc and DCM. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{30}F_2N_3O_4$: 450.2; found: 450.1.

Step 3. Preparation of **17-3:** A mixture of **17-2** (370 mg, 0.761 mmol), Intermediate **D11** (205 mg, 0.761 mmol), HATU (347 mg, 0.914 mmol) and DIPEA (0.795 mL, 4.57 mmol) in DMF (3 mL) was stirred at rt overnight. The mixture was diluted with 100 mL water and extracted with dichloromethane. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product mixture was purified by silica gel chromatography (EtOAc in hexanes: 30%) to give **17-3** (236 mg). In an alternative process, **17-2** and Intermediate **D11** were mixed with EDC and HOBT in the presence of NMM in DMF to give **17-3.** LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{37}H_{51}F_2N_4O_7$: 701.4; found: 701.3.

Step 4. Preparation of **17-4:** A solution of **17-3** (236 mg, 0.34 mmol) in DCE (67 mL) was deoxygenated with argon for 40 minutes. Zhan 1B catalyst (25 mg, 0.034 mmol, Strem) was added and the reaction was heated in a 100 °C oil bath for 40 minutes. Solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (EtOAc in hexanes: 5% to 65%) to give the **17-4** (229 mg). LCMS-ESI$^+$ (*m/z*): $[M-F]^+$ calcd for $C_{35}H_{46}FN_4O_7$: 653.3; found: 653.2.

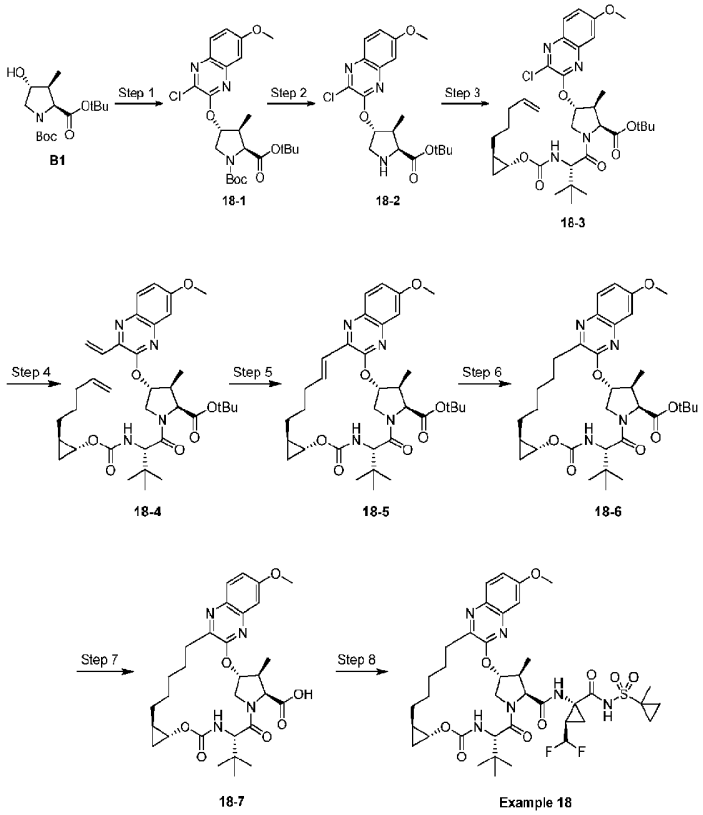
Step 5. Preparation of **17-5:** A solution of **17-4** (229 mg, 0.34 mmol) in 50 mL ethanol was hydrogenated at 1 atm hydrogen gas over 220 mg of 10% wt Pd/C (wet) for 2.5 hours. Filtration through Celite and concentration under reduced pressure gave a crude residue of **17-5** (184 mg). In an alternative process, **17-4** was hydrogenated at hydrogen gas in the presence of Rh. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{35}H_{49}F_2N_4O_7$: 675.4; found: 675.3.

Step 6. Preparation of **17-6:** Ester **17-5** (184 mg, 0.27 mmol) in 2 mL DCM was treated with 1 mL TFA and stirred at rt for 3 h. The reaction mixture was concentrated and then partitioned between water and ethyl acetate. The organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated to give **17-6** (153 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{31}H_{41}F_2N_4O_7$: 619.3; found: 619.2.

Step 7. Preparation of Example **17:** A mixture of carboxylic acid **17-6** (153 mg, 0.247 mmol), Intermediate **A10** (90 mg, 0.297 mmol), HATU (113 mg, 0.297 mmol), DMAP (45 mg, 0.37 mmol) and DIPEA (0.215 mL, 1.24 mmol) in DMF (1.5 mL) was stirred at rt for 40 minutes. The mixture was diluted with 2 N aqueous HCl (2 mL) and extracted with dichloromethane. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product mixture was purified by silica gel chromatography (EtOAc in hexanes: 30% - 95%) to give Example **17** (95 mg). Analytic HPLC RetTime: 8.79 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{40}H_{53}F_4N_6O_9S$: 869.3; found: 869.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.948 (br s, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.29 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.09 (d, *J* = 2.8 Hz, 1H), 6.57 (br s, 1H), 5.97 (td, J_{H-F} = 52 Hz, *J* = 6.8 Hz, 1H), 5.92 (d, *J* = 3.6 Hz, 1H), 5.322 (d, *J* = 9.6 Hz, 1H), 4.42 (ap d, *J* = 7.2 Hz, 1H), 4.40 (ap s, 1H), 4.34 (ap d, *J* = 10 Hz, 1H), 4.08 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.99 - 3.94 (m,

1H), 3.96 (s, 3H), 3.67 (m, 1H), 2.52 (m, 2H), 2.06 (m, 1H), 1.93 (m, 2H), 1.77 (m, 2H), 1.63 (m, 3H), 1.50 (s, 3H), 1.56 - 1.42 (m, 4H), 1.25 (m, 1 H), 1.19 (t, J = 7.2 Hz, 3H), 1.09 (s, 9H), 1.10-0.93 (m, 2H), 0.85 (m, 2H), 0.69 (m, 1H), 0.49 (m, 1 H).

[0204] Example **18.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-14-methoxy-9-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Step 1. Preparation of **18-1:** Intermediate **B1** (1.94 g, 6.44 mmol) was dissolved in MeCN (30 mL) under Ar. Intermediate **E1** (2.02 g, 7.4 mmol) and Cs_2CO_3 (7.5 mmol) were added, and the resulting mixture was stirred for 8 h at rt. Additional Intermediate **E1** (200 mg, 0.73 mmol) and Cs_2CO_3 (245 mg, 0.75 mmol) were added and the reaction mixture was stirred an additional 15 h. The reaction mixture was filtered through Celite with EtOAc and concentrated. The resulting crude residue was dissolved in CH_2Cl_2, concentrated onto 12 g silica gel, and purified by silica gel chromatography (5% to 20% EtOAc in hexanes) to provide **18-1** as a white foam (2.63 g). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{24}H_{33}ClN_3O_6$: 494.2; found: 494.1.

Step 2. Preparation of **18-2:** Substituted quinoxaline **18-1** (905 mg, 1.84 mmol) was dissolved in tert-butyl acetate (7 mL) and CH_2Cl_2 (1.75 mL). $MeSO_3H$ (600 µL, 9.2 mmol) was added dropwise over 45 s, and the resulting yellow solution was stirred at rt for 50 min. Additional $MeSO_3H$ (100 µL, 1.5 mmol) was added in dropwise fashion and the reaction was stirred an additional 10 min. The reaction mixture was transferred to a stirred mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ (30 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford amine **18-2** as a colorless residue (680 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{19}H_{25}ClN_3O_4$: 394.2; found: 394.2.

Step 3. Preparation of **18-3:** Amine **18-2** (680 mg, 1.73 mmol) and Intermediate **D1** (600 mg, 2.1 mmol) were dissolved in DMF (10 mL). DIPEA (925 µL, 5.30 mmol) was added followed by HATU (880 mg, 2.3 mmol). The reaction was stirred 110 min at rt and was diluted with saturated aqueous $NaHCO_3$ (30 mL) and EtOAc (30 mL). The phases were separated and the organic phase was washed with half-saturated brine (2 x 40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to a crude residue. Purification by silica gel chromatography (10% to 20% EtOAc in hexanes) provided **18-3** as a colorless residue (703 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{34}H_{48}ClN_4O_7$: 659.3; found: 659.4.

Step 4. Preparation of **18-4:** A stirred heterogeneous mixture of **18-3** (703 mg, 1.07 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (48 mg, 0.059 mmol) and potassium vinyltrifluoroborate (290 mg, 2.16 mmol) in EtOH (11 mL) was sparged with argon for 15 min. Triethylamine (320 µL, 2.3 mmol) was added and the mixture was heated to 75 °C for 70 min. The reaction mixture was cooled to ambient temperature and was diluted with EtOAc (40 mL) and half-saturated brine (30 mL). The phases were separated and the organic phase was dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (10% to 20% to 30% EtOAc in hexanes) provided **18-4** as a yellow residue (490 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{51}N_4O_7$: 651.4; found: 651.3.

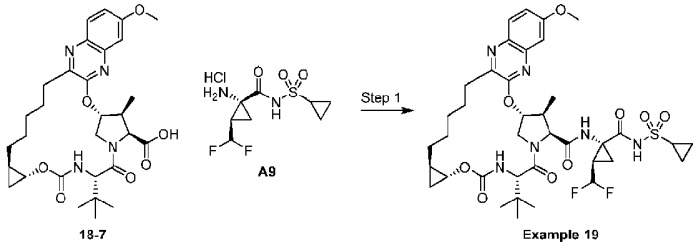
Step 5. Preparation of **18-5: 18-4** (490 mg, 0.179 mmol) was dissolved in DCE (250 mL) and the solution was sparged with Ar for 15 min. Zhan 1B catalyst (66 mg, 0.090 mmol, Strem) was added as a solution in DCE (5 mL) and the resulting solution was stirred at 85 °C under Ar for 105 min. The reaction mixture was cooled to rt and was adsorbed onto silica gel (7.5 g). Purification by silica gel chromatography (10% to 30% EtOAc in hexanes) provided **18-5** as an amorphous residue (290 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{47}N_4O_7$: 623.3; found: 623.3.

Step 6: Preparation of **18-6:** Olefin **18-5** (290 mg, 0.072 mmol) was dissolved in EtOAc (5.5 mL) and EtOH (5.5 mL) and the reaction vessel was purged with Ar. Pd/C (10 wt % Pd, 92 mg) was added in a single portion and the reaction vessel was purged twice with H_2. The reaction was stirred at rt under 1 atm H_2 for 1.5 h and was filtered through a pad of Celite and concentrated to afford a crude residue of **18-6** that was used without further purification (LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{34}H_{49}N_4O_7$: 625.4; found: 625.0.

Step 7. Preparation of **18-7: 18-6** (0.466 mmol) was dissolved in CH_2Cl_2 (4.3 mL) under Ar. TMSOTf (210 µL, 1.16 mmol) was added dropwise over 30 s. The reaction was stirred 65 min and an additional portion of TMSOTf (50 µL, 0.28 mmol) was added. The reaction was stirred an additional 100 min and an additional portion of TMSOTf (100 µL, 0.55 mmol) was added. The reaction was stirred an additional 105 min and was concentrated *in vacuo*. The resulting crude residue was dissolved in CH_2Cl_2 (20 mL) and 0.2 M aqueous NaOH (10 mL) was added. The mixture was stirred for 5 min and was acidified with 1 M aqueous HCl (20 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated to afford **18-7** as a brown solid (273 mg). LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{30}H_{41}N_4O_7$: 569.3; found: 568.9.

Step 8. Preparation of Example **18:** To a suspension of acid **18-7** (28 mg, 0.049 mmol) and Intermediate **A10** (26.5 mg, 0.087 mmol) in MeCN (1.3 mL) was added DIPEA (55 µL, 0.31 mmol). To the resulting solution was added HATU (30.5 mg, 0.080 mmol). The reaction was stirred at rt for 1 h and an additional portion of Intermediate **A10** (3 mg, 0.01 mmol) was added. After an additional 15 min, the reaction was diluted with EtOAc (30 mL) and 1 M aqueous HCl (20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (30 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue. Purification by silica gel chromatography (10% to 40% acetone in hexanes) provided an amorphous residue that was lyophilized from water and MeCN to provide Example **18** as a white amorphous solid (26.4 mg). Analytic HPLC RetTime: 8.42 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for$C_{39}H_{53}F_2N_6O_9S$: 819.4 ; found: 819.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.82 (d, *J* = 9.1 Hz, 1H), 7.19 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.08 (d, *J* = 2.6 Hz, 1H), 6.86 (s, 1H), 6.14 - 5.70 (m, 1H), 5.65 (d, *J* = 9.9 Hz, 1H), 5.56 - 5.50 (m, 1H), 4.53 - 4.40 (m, 3H), 4.12 (dd, *J* = 11.9, 4.3 Hz, 1H), 3.93 (s, 3H), 3.81 - 3.74 (m, 1H), 3.06 - 2.64 (m, 4H), 2.10 - 1.35 (m, 13H), 1.13 (d, *J* = 7.5 Hz, 3H), 1.09 (s, 9H), 1.04 - 0.65 (m, 6H), 0.52 - 0.41 (m, 1H).

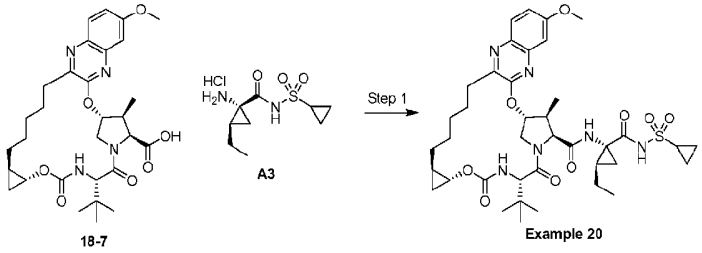
[0205] Example **19.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-14-methoxy-9-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



[0206] Step 1. Preparation of Example **19:** To a suspension of acid **18-7** (8.8 mg, 0.015 mmol) and Intermediate **A9** (7.4 mg,

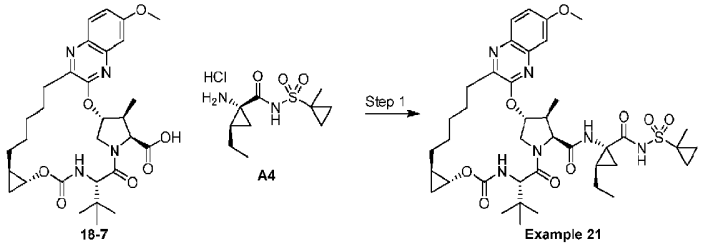
0.025 mmol) in MeCN (0.5 mL) was added DIPEA (14 µL, 0.08 mmol). To the resulting solution was added HATU (9.1 mg, 0.024 mmol). The reaction was stirred at rt for 1 h and an additional portion of Intermediate **A9** (5 mg, 0.02 mmol) and HATU (5 mg, 0.01 mmol) were added. After an additional 1.5 h, the reaction was diluted with EtOAc (30 mL), 0.2 M aqueous HCl (10 mL), and brine (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (30 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue. Purification by silica gel chromatography (10% to 40% acetone in hexanes) provided a residue that was lyophilized from water and MeCN to provide Example **19** as a white amorphous solid (8.5 mg). Analytic HPLC RetTime: 8.69 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{38}H_{51}F_2N_6O_9S$: 805.3 ; found: 805.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.83 (d, *J* = 9.1 Hz, 1H), 7.19 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 6.77 (s, 1 H), 6.25 - 5.76 (m, 1H), 5.57 (d, *J* = 3.7 Hz, 1 H), 5.51 (d, *J* = 9.9 Hz, 1H), 4.49 - 4.37 (m, 3H), 4.13 (dd, *J* = 12.2, 4.3 Hz, 1 H), 3.94 (s, 3H), 3.79 - 3.72 (m, 1H), 3.01 - 2.69 (m, 4H), 2.13 - 2.06 (m, 1H), 2.01 - 1.22 (m, 9H), 1.14 (d, *J* = 7.2 Hz, 3H), 1.09 (s, 9H), 1.06 - 0.82 (m, 6H), 0.76 - 0.62 (m, 1H), 0.54 - 0.41 (m, 1H).

[0207] Example **20.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-{(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethylcyclopropyl}-14-methoxy-9-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



[0208] Step 1. Preparation of Example **20:** To a suspension of acid **18-7** (10 mg, 0.018 mmol) and Intermediate **A3** (6.3 mg, 0.023 mmol) in MeCN (0.5 mL) was added DIPEA (15 µL, 0.086 mmol). To the resulting solution was added HATU (9.0 mg, 0.024 mmol). The reaction was stirred at rt for 2.5 h and an additional portion of Intermediate **A3** (6.5 mg, 0.024 mmol) was added. After an additional 45 min, the reaction was diluted with EtOAc (2 mL) and 1 M aqueous HCl (1.5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (4 x 1.5 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue. Purification by silica gel chromatography (20% to 25% to 30% acetone in hexanes) provided a residue that was lyophilized from water and MeCN to provide Example **20** as a white amorphous solid (8.0 mg). Analytic HPLC RetTime: 8.40 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{39}H_{55}N_6O_9S$: 783.4; found: 783.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.83 (d, *J* = 9.1 Hz, 1H), 7.19 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 6.42 (s, 1H), 5.57 (d, *J* = 3.8 Hz, 1 H), 5.36 (d, *J* = 9.9 Hz, 1H), 4.48 - 4.34 (m, 3H), 4.11 (dd, *J* = 11.8, 4.1 Hz, 1H), 3.94 (s, 3H), 3.79 - 3.72 (m, 1H), 2.98 - 2.68 (m, 4H), 1.95 - 0.80 (m, 33H), 0.76 - 0.61 (m, 1H), 0.53 - 0.41 (m, 1 H).

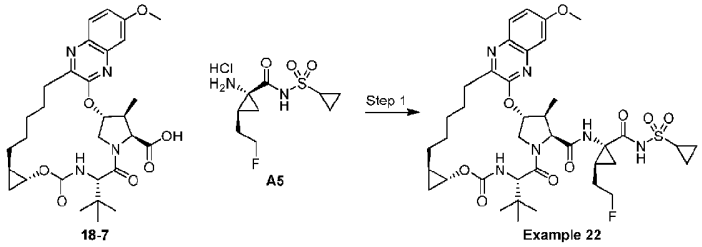
[0209] Example **21.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-ethyl-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-14-methoxy-9-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



[0210] Step 1. Preparation of Example **21:** To a suspension of acid **18-7** (94.9 mg, 0.167 mmol) and Intermediate **A4** (74.5 mg, 0.263 mmol) in MeCN (2.5 mL) was added DIPEA (180 µL, 1.0 mmol). To the resulting solution was added HATU (9.0 mg, 0.024 mmol). The reaction was stirred at rt for 110 min and additional portions of Intermediate **A4** (31 mg, 0.11 mmol) and DIPEA (50 µL, 0.29 mmol) were added. After an additional 40 min, the reaction was diluted with EtOAc (30 mL), 0.2 M aqueous HCl (20 mL), and brine (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue. Purification by silica gel chromatography

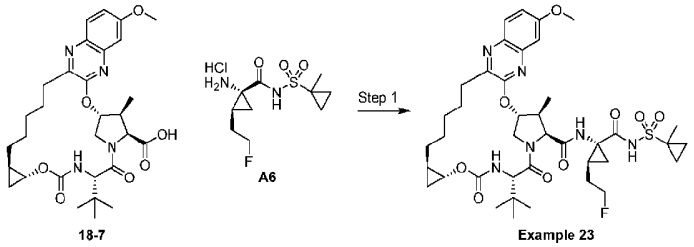
(10% to 40% acetone in hexanes) provided a residue that was lyophilized from water and MeCN to provide Example **21** as a white amorphous solid (102.1 mg). Analytic HPLC RetTime: 8.83 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{40}H_{57}N_6O_9S$: 797.4; found: 797.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1 H), 7.80 (d, *J* = 9.1 Hz, 1H), 7.17 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.07 (d, *J* = 2.7 Hz, 1H), 6.92 (s, 1H), 5.58 - 5.42 (m, 2H), 4.48 - 4.36 (m, 3H), 4.09 (dd, *J* = 11.8, 4.2 Hz, 1H), 3.92 (s, 3H), 3.79 - 3.74 (m, 1H), 2.97 - 2.66 (m, 4H), 1.80 - 0.88 (m, 33H), 0.84 - 0.77 (m, 1H), 0.77 - 0.61 (m, 2H), 0.52 - 0.40 (m, 1H).

[0211] Example **22.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2S)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(2-fluoroethyl)cyclopropyl]-14-methoxy-9-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



[0212] Step 1. Preparation of Example **22:** To a suspension of acid **18-7** (30.1 mg, 0.0529 mmol) and Intermediate **A5** (35 mg, 0.12 mmol) in MeCN (0.5 mL) was added DIPEA (85 µL, 0.49 mmol). To the resulting solution was added HATU (34.5 mg, 0.0907 mmol). The reaction was stirred at rt for 90 min and was diluted with EtOAc (30 mL), 0.2 M aqueous HCl (20 mL), and brine (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (30 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue that was dissolved in CH_2Cl_2 and adsorbed onto 2 g silica gel. Purification by silica gel chromatography (15% to 55% acetone in hexanes) provided a residue that was lyophilized from water and MeCN to provide Example **22** as a white amorphous solid (35.5 mg). Analytic HPLC RetTime: 8.54 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{39}H_{54}FN_6O_9S$: 801.4; found: 801.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.82 (d, *J* = 9.1 Hz, 1H), 7.19 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.08 (d, *J* = 2.7 Hz, 1H), 6.68 (s, 1H), 5.56 (d, *J* = 3.9 Hz, 1 H), 5.43 (d, *J* = 9.9 Hz, 1H), 4.57 - 4.29 (m, 5H), 4.12 (dd, *J* = 11.8, 4.1 Hz, 1H), 3.93 (s, 3H), 3.78 - 3.71 (m, 1H), 2.97 - 2.67 (m, 4H), 2.12 - 1.25 (m, 14H), 1.15 (d, *J* = 7.4 Hz, 3H), 1.10 (s, 9H), 1.06 - 0.89 (m, 4H), 0.76 - 0.62 (m, 1H), 0.53 - 0.42 (m, 1 H).

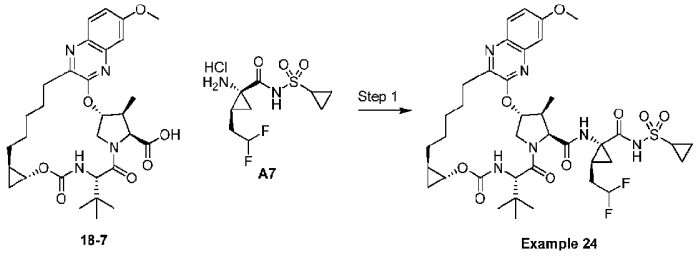
[0213] Example **23.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2S)-2-(2-fluoroethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-14-methoxy-9-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



[0214] Step 1. Preparation of Example **23:** To a suspension of acid **18-7** (30.5 mg, 0.0536 mmol) and Intermediate **A6** (24.8 mg, 0.0824 mmol) in MeCN (0.5 mL) was added DIPEA (60 µL, 0.34 mmol). To the resulting solution was added HATU (32.3 mg, 0.0850 mmol). The reaction was stirred at rt for 75 min and an additional portion of Intermediate **A6** (9 mg, 0.03 mmol) was added. After an additional 75 min the reaction was diluted with EtOAc (30 mL), 0.2 M aqueous HCl (20 mL), and brine (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (30 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue that was dissolved in CH_2Cl_2 and adsorbed onto 2 g silica gel. Purification by silica gel chromatography (15% to 55% acetone in hexanes) provided a residue that was lyophilized from water and MeCN to provide Example **23** as a white amorphous solid (37.1 mg). Analytic HPLC RetTime: 8.64 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{40}H_{56}FN_6O_9S$: 815.4; found: 815.6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.83 (d, *J* = 9.1 Hz, 1H), 7.20 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.10 (d, *J* = 2.7 Hz, 1H), 6.75 (s, 1H), 5.56 (d, *J* = 3.9 Hz, 1 H), 5.50 (d, *J* = 10.0 Hz, 1H), 4.56 - 4.34 (m, 5H), 4.13 (dd, *J* = 11.8, 4.2 Hz, 1 H), 3.95 (s, 3H), 3.82 - 3.75 (m, 1H), 2.98 - 2.70 (m, 4H), 2.07 - 2.00 (m, 1 H), 2.00 - 1.93 (m, 1H), 1.88 - 1.44 (m, 12H), 1.32 - 1.26 (m, 1H), 1.17 (d, *J* = 7.4 Hz, 3H), 1.12 (d, *J* = 10.6 Hz, 9H), 1.07 - 0.83 (m, 4H), 0.81 - 0.65 (m, 2H),

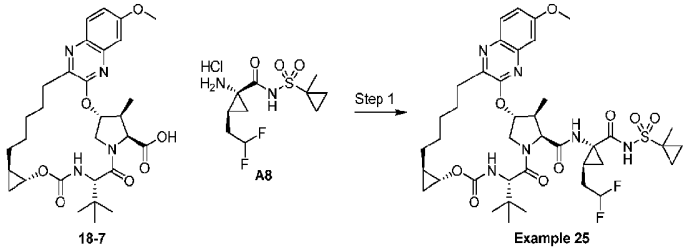
0.52 - 0.44 (m, 1 H).

[0215] Example **24.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2S)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(2,2-difluoroethyl)cyclopropyl]-14-methoxy-9-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



[0216] Step 1. Preparation of Example **24:** To a suspension of acid **18-7** (30.2 mg, 0.0531 mmol) and Intermediate **A7** (25.9 mg, 0.0850 mmol) in MeCN (0.5 mL) was added DIPEA (60 µL, 0.34 mmol). To the resulting solution was added HATU (32 mg, 0.084 mmol). The reaction was stirred at rt for 75 min and an additional portion of Intermediate **A7** (3.0 mg, 0.0098 mmol) was added. After an additional 30 min the reaction was diluted with EtOAc (30 mL), 0.2 M aqueous HCl (20 mL), and brine (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (30 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue that was dissolved in CH_2Cl_2 and adsorbed onto 2 g silica gel. Purification by silica gel chromatography (15% to 55% acetone in hexanes) provided a residue that was lyophilized from water and MeCN to provide Example **24** as a white amorphous solid (35.5 mg). Analytic HPLC RetTime: 8.62 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{39}H_{53}F_2N_6O_9S$: 819.4; found: 819.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.82 (d, *J* = 9.1 Hz, 1 H), 7.19 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.08 (d, *J* = 2.7 Hz, 1H), 6.69 (s, 1H), 5.99 - 5.64 (m, 1 H), 5.56 (d, *J* = 3.9 Hz, 1H), 5.40 (d, *J* = 10.0 Hz, 1H), 4.47 - 4.39 (m, 3H), 4.14 - 4.08 (m, 1H), 3.93 (s, 3H), 3.78 - 3.72 (m, 1H), 2.96 - 2.67 (m, 4H), 2.29 - 2.16 (m, 2H), 1.83 - 1.24 (m, 12H), 1.15 (d, *J* = 7.4 Hz, 3H), 1.09 (s, 9H), 1.05 - 0.82 (m, 4H), 0.74 - 0.63 (m, 1H), 0.53 - 0.42 (m, 1H).

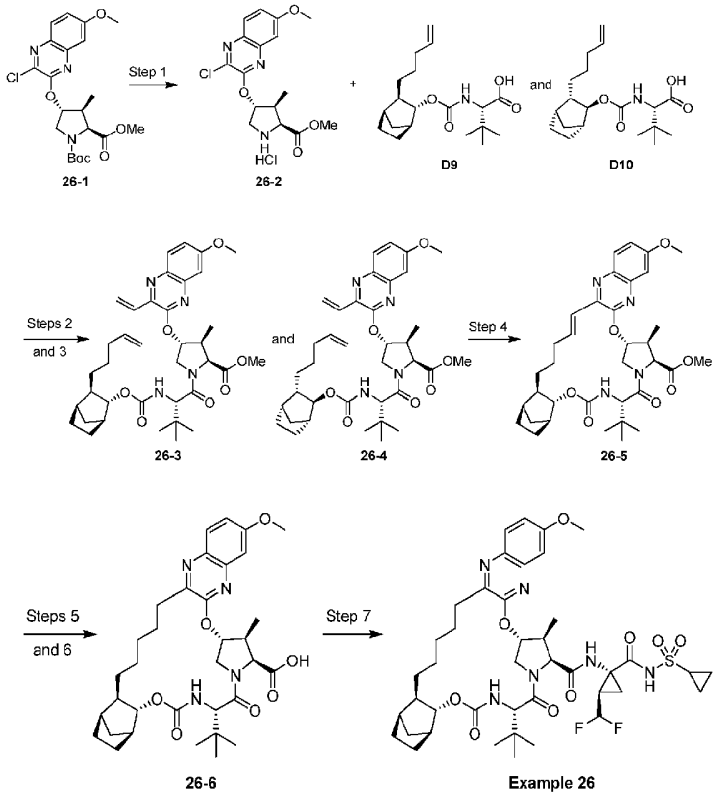
[0217] Example **25.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2S)-2-(2,2-difluoroethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-14-methoxy-9-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



[0218] Step 1. Preparation of Example **25:** To a suspension of acid **18-7** (30.3 mg, 0.0532 mmol) and Intermediate **A8** (28.3 mg, 0.0887 mmol) in MeCN (0.5 mL) was added DIPEA (60 µL, 0.34 mmol). To the resulting solution was added HATU (32.4 mg, 0.0852 mmol). The reaction was stirred at rt for 2.5 h and was diluted with EtOAc (30 mL), 0.2 M aqueous HCl (20 mL), and brine (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (30 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue that was dissolved in CH_2Cl_2 and adsorbed onto 2 g silica gel. Purification by silica gel chromatography (15% to 55% acetone in hexanes) provided a residue that was lyophilized from water and MeCN to provide Example **25** as a white amorphous solid (33.9 mg). Analytic HPLC RetTime: 8.66 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{40}H_{55}F_2N_6O_9S$: 833.4; found: 833.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.82 (d, *J* = 9.1 Hz, 1H), 7.18 (dd, *J* = 9.1, 2.8 Hz, 1 H), 7.08 (d, *J* = 2.7 Hz, 1 H), 6.64 (s, 1H), 6.04 - 5.66 (m, 1 H), 5.54 (d, *J* = 4.0 Hz, 1H), 5.47 (d, *J* = 10.0 Hz, 1H), 4.50 - 4.38 (m, 3H), 4.11 (dd, *J* = 11.8, 4.2 Hz, 1H), 3.93 (s, 3H), 3.82 - 3.71 (m, 1H), 2.98 - 2.68 (m, 4H), 2.27 - 2.11 (m, 2H), 1.96 - 1.41 (m, 12H), 1.32 (dd, *J* = 9.6, 5.4 Hz, 1H), 1.15 (d, *J* = 7.4 Hz, 3H), 1.10 (s, 9H), 1.05 - 0.64 (m, 6H), 0.51 - 0.42 (m, 1H).

[0219] Example **26.** Preparation of (1R,4S,4aR,8S,11S,12S,13R,25aR)-8-tert-butyl-N-[(1 R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-17-methoxy-12-methyl-6,9-dioxo-

2,3,4,4a,6,7,8,9,12,13,21,22,23,24,25,25a-hexadecahydro-1H,11H-1,4:10,13-dimethanoquinoxalino[2,3-k][1,10,3,6]benzodioxadiazacyclononadecine-11-carboxamide.



Step 1. Preparation of **26-2:** To a solution of **26-1** (311 mg, 0.710 mmol; prepared similarly to **18-1** of Example **18** substituting Intermediate **B2** for Intermediate **B1** in step 1) in dioxane (1.8 mL) was added 4 M HCl in dioxane (1.8 mL, 7.2 mmol). The reaction was stirred for 15.5 h at rt and was then concentrated under reduced pressure to give **26-2** as a white amorphous solid that was used without further purification in the following step. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{16}H_{19}ClN_3O_4$: 352.1; found: 352.2.

Steps 2 and 3. Preparation of diastereomeric mixture **26-3** and **26-4:** Amine hydrochloride **26-2** (0.710 mmol) was dissolved along with 1:1 mixture of Intermediate mixture **D9** and **D10** (266 mg, 0.788 mmol) and DIPEA (600 µL, 3.4 mmol) in DMF (4.5 mL). HATU (360 mg, 0.95 mmol) was added in one portion. The reaction was stirred 1.75 h at rt and was diluted with saturated aqueous $NaHCO_3$ (20 mL), water (10 mL) and EtOAc (30 mL). The phases were separated and the organic phase was washed twice with a mixture of water (30 mL) and brine (5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to a crude residue that was purified by silica gel chromatography (10% to 30% EtOAc in hexanes) to provide a colorless residue (380 mg; LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{35}H_{48}ClN_4O_7$: 671.3; found: 671.6). A stirred heterogeneous mixture of this residue, $PdCl_2(dppf)\cdot CH_2Cl_2$ (35 mg, 0.043 mmol) and potassium vinyltrifluoroborate (156 mg, 1.16 mmol) in EtOH (7 mL) was sparged with argon for several minutes. Triethylamine (170 µL, 1.2 mmol) was added and the mixture was heated to 70 °C for 55 min. The reaction mixture was cooled to ambient temperature, diluted with EtOAc (40 mL), and washed with water (30 mL). The organics were dried over anhydrous Na_2SO_4, filtered and concentrated to afford a residue that was purified by silica gel chromatography (15% to 30% EtOAc in hexanes) to afford diastereomeric mixture **26-3** and **26-4** as a yellow residue (277 mg). LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{37}H_{51}N_4O_7$: 663.4; found: 663.3.

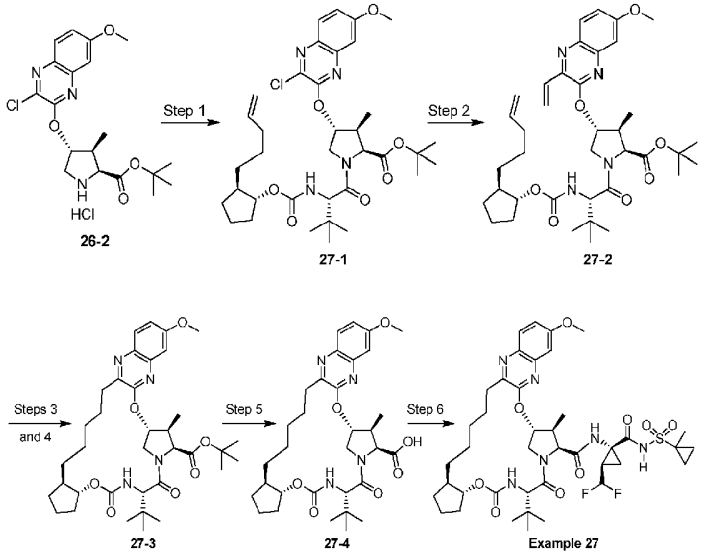
Step 4. Preparation of **26-5:** Diastereomeric mixture **26-3** and **26-4** (277 mg, 0.419 mmol) was dissolved in DCE (140 mL) and the solution was sparged with Ar for 15 min. Zhan 1B catalyst (37 mg, 0.050 mmol, Strem) was added and the resulting solution was stirred at 85 °C under Ar for 1.5 h. The reaction mixture was then concentrated and purified by silica gel chromatography (20% to 50% EtOAc in hexanes) to afford **26-5** as an amorphous residue (105 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{35}H_{47}N_4O_7$: 635.3; found: 635.3.

Steps 5 and 6. Preparation of **26-6:** To a solution of **26-5** (105 mg, 0.165 mmol) in 1:1 EtOAc:EtOH (4 mL) was added Pd/C (10 wt % Pd, 43 mg). The reaction vessel was purged twice with H_2 and was stirred at rt under 1 atm H_2 for 1 h. The reaction mixture was filtered through a pad of Celite and concentrated to afford a crude residue (106 mg; LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for

$C_{35}H_{49}N_4O_7$: 637.4; found: 637.3). This residue was then dissolved in THF (0.8 mL). MeOH (0.4 mL), water (0.4 mL) and $LiOH•H_2O$ (67 mg, 1.6 mmol) were added and the mixture was stirred at 45 °C for 14.5 h. The reaction was quenched dropwise with 1 N aqueous HCl (1.3 mL) and was diluted with CH_2Cl_2 (30 mL) and 1 N aqueous HCl (20 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (30 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated to afford **26-6** as a residue (93.8 mg) that was used directly in Step 7. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{34}H_{47}N_4O_7$: 623.3; found: 623.3.

Step 7. Preparation of Example **26:** To a suspension of acid **26-6** (93.8 mg, 0.151 mmol) and Intermediate **A9** (58 mg, 0.20 mmol) in MeCN was added DIPEA (120 µL, 0.69 mmol). To the resulting solution was added HATU (73.5 mg, 0.193 mmol). The reaction was stirred at rt for 100 min and an additional portion of Intermediate **A9** (6 mg, 0.02 mmol) was added. After an additional 30 min, additional Intermediate **A9** (9 mg, 0.03 mmol), HATU (9 mg, 0.02 mmol) and DIPEA (10 µL, 0.06 mmol) were added. The reaction was stirred for an additional 50 min and was diluted with EtOAc (25 mL), 0.2 M aqueous HCl (20 mL) and brine (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (25 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue. Purification by silica gel chromatography (25% to 40% acetone in hexanes) provided an amorphous residue that was lyophilized from water and MeCN to provide Example **26** as a white amorphous solid (113 mg). Analytic HPLC RetTime: 9.19 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{42}H_{57}F_2N_6O_9S$: 859.4; found: 859.2. ^1H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.80 (d, *J* = 9.1 Hz, 1H), 7.21 - 7.15 (m, 2H), 7.07 (d, *J* = 2.7 Hz, 1H), 6.13 - 5.79 (m, 1H), 5.63 (d, *J* = 10.1 Hz, 1H), 5.50 - 5.45 (m, 1H), 4.51 (d, *J* = 10.1 Hz, 1H), 4.44 (d, *J* = 7.4 Hz, 1H), 4.25 (s, 1H), 4.18 - 4.12 (m, 2H), 3.93 (s, 3H), 3.02 - 2.77 (m, 3H), 2.66 - 2.57 (m, 1H), 2.18 - 0.90 (m, 36H).

[0220] Example 27. Preparation of (3aR,7S,10S,11S,12R,24aR)-7-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-16-methoxy-11-methyl-5,8-dioxo-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10h-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide.



Step 1. Preparation of 27-1: Amine hydrochloride 26-2 (217 mg, 0.504 mmol), was treated with BEP (207 mg, 0.756 mmol), Intermediate D5 (283 mg, 0.909 mmol), EtOAc (9 mL), NMP (1 mL) and DIPEA (0.44 mL, 2.5 mmol), then heated to 50 °C. After 1.5 h, the reaction mixture was diluted with EtOAc. The organic solution was washed successively with saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (9% to 40% EtOAc/Hex) to afford amide **27-1** (235 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{36}H_{52}ClN_4O_7$: 687.35; found: 688.13.

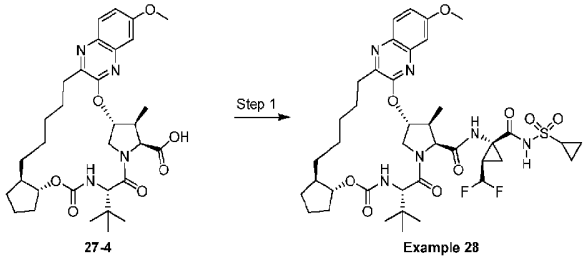
Step 2. Preparation of **27-2:** Amide **27-1** (235 mg, 0.342 mmol) was treated with potassium vinyltrifluoroborate (69 mg, 0.513 mmol), $Pd(dppf)Cl_2$•DCM (28 mg, 0.0342 mmol), EtOH (3.4 mL) and TEA (0.072 mL, 0.513 mmol), then heated to reflux. After 50 min, the reaction mixture was diluted with EtOAc and washed with H_2O and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (9% to 40% EtOAc/Hex) to afford vinyl quinoxaline **27-2** (219 mg). LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{38}H_{55}N_4O_7$: 679.41; found: 679.49.

Steps 3 and 4. Preparation of **27-3:** Vinyl quinoxaline **27-2** (219 mg, 0.323 mmol) was suspended in DCE (65 mL) and treated with Zhan 1B catalyst (41 mg, 0.065 mmol, Strem). The suspension was deoxygenated with bubbling N_2 for 17 min, then heated to reflux for 90 min. The reaction mixture was then filtered over Celite and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (15% to 50% EtOAc/Hex) to afford the desired macrocycle (165 mg; LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{51}N_4O_7$: 651.38; found: 651.40). The macrocyclic product of step 3 was dissolved in EtOH (10 mL) and EtOAc (2 mL) and treated with 10 wt % Pd/C (95 mg). Hydrogen from a balloon was bubbled through the suspension for 1 min and the mixture was stirred under H_2 (1 atm) for an additional 1.5 h. The reaction mixture was filtered over Celite and concentrated under reduced pressure to afford the desired macrocycle **27-3** which was carried on without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{53}N_4O_7$: 653.39; found: 653.32.

Step 5. Preparation of **27-4:** The crude product of step 4 was dissolved in DCM and treated with TMSOTf (0.23 mL, 1.3 mmol). After stirring at rt for 1 h 15 min, the reaction mixture was concentrated under reduced pressure. The residue was redissolved in DCM and added by pipette to a separatory funnel containing 1 M aqueous NaOH. The mixture was agitated for 1 min, then acidified to pH 1-2 with 10% aqueous HCl. The aqueous layer was extracted three times with DCM and combined organics dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography to afford carboxylic acid **27-4** (119 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{32}H_{45}N_4O_7$: 597.33; found: 597.40.

Step 6. Preparation of Example **27:** Carboxylic acid **27-4** (105 mg, 0.177 mmol) and Intermediate **A10** (65 mg, 0.212 mmol) were treated with TBTU (68 mg, 0.212 mmol), DMAP (26 mg, 0.212 mmol), DCM (1.8 mL) and DIPEA (0.31 mL, 1.8 mmol). The reaction mixture was stirred at rt for 30 min, then more amine **A10** (40 mg, 0.131 mmol) was added and the reaction mixture was heated to reflux. After an additional 1.25 h, the mixture was concentrated under reduced pressure. The crude residue was purified by HPLC to afford Example **27** (80 mg) in approximately 90% purity as a TFA salt. Analytic HPLC RetTime: 9.06 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{41}H_{57}F_2N_6O_9S$: 847.39; found: 847.69. ^{1}H NMR (400 MHz, CD_3OD) δ 9.23 (s, 1H), 7.87 - 7.72 (m, 1H), 7.31 - 7.14 (m, 2H), 5.84 (td, *J* = 55.6, 6.5 Hz, 1 H), 5.58 (d, *J* = 22.6 Hz, 1H), 4.94 - 4.81 (m, 1H), 4.37 (d, *J* = 15.8 Hz, 1 H), 4.29 - 4.10 (m, 2H), 3.94 (s, 3H), 3.01 (ddd, *J* = 15.1, 9.9, 5.3 Hz, 1H), 2.84 (p, *J* = 7.4 Hz, 1H), 2.75 (ddd, *J* = 13.3, 10.2, 6.0 Hz, 1 H), 2.03 (d, *J* = 9.0 Hz, 2H), 1.97 - 1.74 (m, 4H), 1.73 - 1.55 (m, 6H), 1.53 (s, 3H), 1.48 - 1.21 (m, 8H), 1.19 - 1.02 (m, 14H), 0.99 - 0.80 (m, 2H).

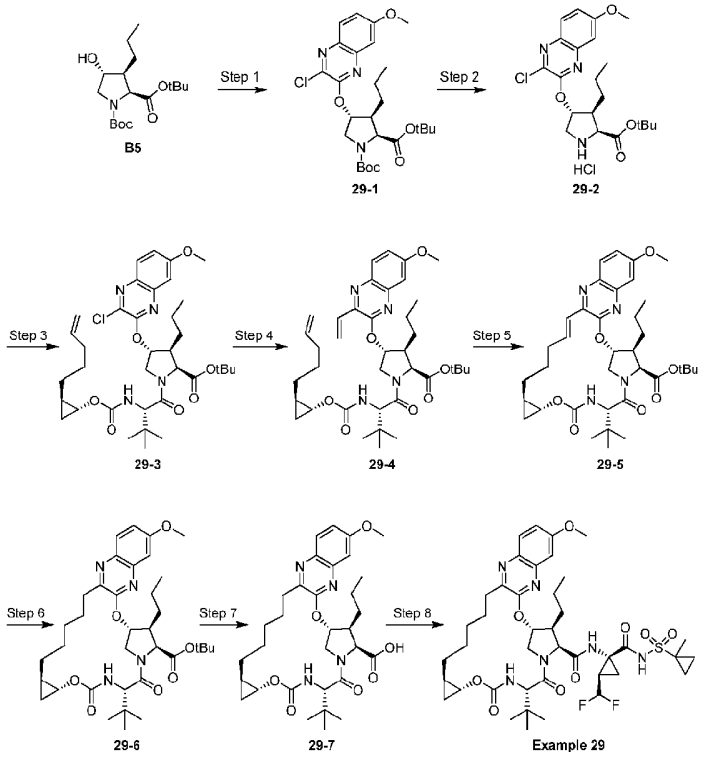
[0221] Example 28. Preparation of (3aR,7S,10S,11S,12R,24aR)-7-tert-butyl-N-[(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-16-methoxy-11-methyl-5,8-dioxo-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10H-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide.



27-4 **Example 28**

[0222] Step 1. Carboxylic acid **27-4** (20 mg, 0.034 mmol) and Intermediate **A9** (35 mg, 0.12 mmol) were treated with TBTU (22 mg, 0.067 mmol), DMAP (8 mg, 0.07 mmol), DCM (1 mL) and DIPEA (0.117 mL, 0.674 mmol). The reaction mixture was stirred at rt for 15 h, then concentrated under reduced pressure. The crude residue was purified by HPLC to afford Example **28** (22 mg) in approximately 90% purity as a TFA salt. Analytic HPLC RetTime: 8.90 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{40}H_{55}F_2N_6O_9S$: 833.37; found: 833.61. ^{1}H NMR (400 MHz, CD_3OD) δ 9.23 (s, 1H), 7.79 (d, *J* = 8.8 Hz, 1 H), 7.34 - 7.10 (m, 2H), 5.86 (td, *J* = 55.8, 6.5 Hz, 1H), 5.61 (s, 1 H), 4.54 (t, *J* = 9.7 Hz, 1H), 4.36 (d, *J* = 16.5 Hz, 1H), 4.28 - 4.07 (m, 2H), 3.95 (d, *J* = 17.8 Hz, 3H), 3.08 - 2.91 (m, 2H), 2.90 - 2.79 (m, 1H), 2.73 (ddd, *J* = 13.3, 10.3, 6.0 Hz, 1H), 2.04 (s, 2H), 1.97 - 1.74 (m, 4H), 1.64 (ddd, *J* = 18.7, 11.6, 4.0 Hz, 4H), 1.49 - 1.19 (m, 11 H), 1.18 - 0.94 (m, 14H), 0.94 - 0.80 (m, 1 H).

[0223] Example **29.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-14-methoxy-3,6-dioxo-9-propyl-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Step 1. Preparation of **29-1:** To a solution of Intermediate **B5** (188 mg, 0.57 mmol) and Intermediate **E1** (233 mg, 0.86 mmol) in MeCN (2.85 mL) was added cesium carbonate (280 mg, 9.18 mmol) at rt under an argon atmosphere. After 19 h, the reaction mixture was then filtered through a pad of Celite and the filtrate concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford substituted quinoxaline **29-1** (240 mg) as a colorless oil. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{26}H_{37}ClN_3O_6$: 522.2; found: 522.3.

Step 2. Preparation of **29-2:** To a solution **29-1** (240 mg, 0.46 mmol) in dioxane (1 mL) was added 4 M hydrochloric acid in dioxane (4 mL, 1 mmol) and the reaction stirred at rt. After 15 h, the reaction mixture was concentrated *in vacuo* to afford amine hydrochloride **29-2** (200 mg) as an off white solid, which was used directly in the next step without further purification. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{21}H_{29}ClN_3O_4$: 422.2; found: 422.2.

Step 3. Preparation of **29-3:** To a solution of **29-2** (200 mg, 0.46 mmol) and Intermediate **D1** (170 mg, 0.51 mmol) in MeCN (2.3 mL) was added HATU (192 mg, 0.51 mmol) followed by DIPEA (400 µL, 2.30 mmol) at rt under and argon atmosphere. After 1.5 h, the reaction mixture was concentrated *in vacuo,* and the crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford amide **29-3** (67 mg) as a colorless oil. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{36}H_{52}ClN_4O_7$: 687.3; found: 687.5.

Step 4. Preparation of **29-4:** To a solution of **29-3** (67 mg, 98 µmol), TEA (20 µL, 150 µmol) and potassium vinyltrifluoroborate (19.7 mg, 150 µmol) in EtOH (500 µL) was added PdCl2(dppf) (8 mg, 9.8 µmol). The reaction mixture was deoxygenated with argon for 10 min and was heated to 78 °C. After 40 min, the reaction mixture was allowed to cool to rt and was concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford vinyl quinoxaline **29-4** (40.2 mg) as a colorless oil. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{38}H_{55}N_4O_7$: 679.4; found: 679.6.

Step 5. Preparation of **29-5:** To a solution of **29-4** (40 mg, 59 µmol) in DCE (11.8 mL) was added Zhan 1B catalyst (4 mg, 6 µmol, Strem) and the reaction mixture was degassed for 10 minutes with argon. The reaction mixture was then heated to 100 °C. After 1 h, the reaction mixture was allowed to cool to rt and was concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford macrocycle **29-5** (31 mg) as a light yellow oil. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{36}H_{51}N_4O_7$: 651.4; found: 651.5.

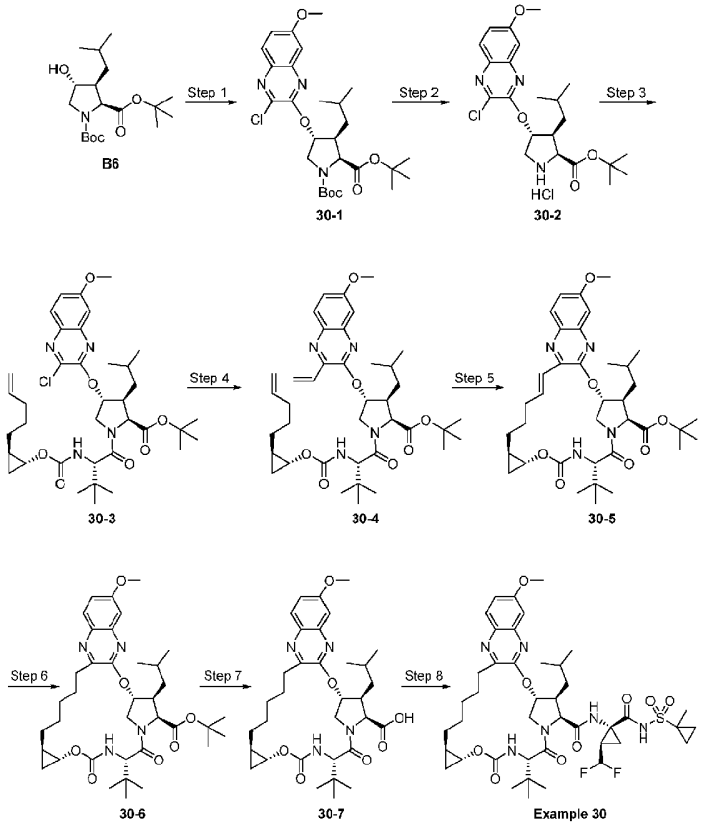
Step 6. Preparation of **29-6:** To a solution of macrocycle **29-5** (31 mg, 47 µmol) in ethanol (500 µL) was added Pd/C (10 wt %, 5 mg, 5 µmol) at rt under an argon atmosphere. The reaction vessel was evacuated and refilled with 1 atm hydrogen gas (3 x) and the reaction mixture was stirred vigorously at rt. After 1 h, the reaction mixture was diluted with ethyl acetate (10 mL) and was

filtered through a pad of Celite with ethyl acetate washings (3 × 5 mL). The filtrate was concentrated *in vacuo* to afford macrocycle **29-6** (31 mg), which was used directly in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{53}N_4O_7$: 653.4; found: 653.5.

Step 7. Preparation of **29-7:** To a solution of **29-6** (31 mg, 47 µmol) in DCM (0.5 mL) was added TMSOTf (44 µL, 0.25 mmol) at rt under an argon atmosphere. After 25 min, the reaction mixture was concentrated *in vacuo* and was azeotropically dried from toluene (2 × 2 mL) to afford carboxylic acid **29-7** (35 mg) as a yellow oil, which was used directly in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{45}N_4O_7$: 597.3; found: 597.4.

Step 8. Preparation of Example **29:** To a solution of **29-7** (35 mg, 49 µmol) and Intermediate **A10** (22 mg, 74 µmol) in MeCN (245 µL) was added HATU (28 mg, 74 µmol) followed by DIPEA (43 µL, 250 µmol) at rt under an argon atmosphere. After 3 h, the reaction mixture was concentrated *in vacuo,* was purified by preparatory HPLC (Gemini 5u C18 110Å column, 5-100% MeCN/H_2O, 0.1% trifluoroacetic acid modifier) and was lyophilized to afford Example **29** (22.3 mg) as a white powder TFA salt. Analytic HPLC RetTime: 8.81 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{41}H_{56}F_2N_6O_9S$: 847.4; found: 847.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (d, *J* = 9.4 Hz, 1 H), 7.93 (d, *J* = 9.1 Hz, 1 H), 7.36 (d, *J* = 9.1 Hz, 1H), 7.21 (d, *J* = 11.0 Hz, 1 H), 7.14 (s, 1 H), 5.97 (td, J_{H-F} = 55 Hz, *J* = 7.2 Hz, 1 H), 5.84 (br s, 1 H), 5.41 (d, *J* = 9.4 Hz, 1 H), 4.66 - 4.34 (m, 3H), 4.13 (app d, *J* = 11.8 Hz, 1 H), 4.08 (s, 1 H), 3.97 (s, 3H), 3.78 - 3.71 (m, 1 H), 3.09 - 2.65 (m, 5H), 2.14 - 2.04 (m, 1 H), 1.87 - 1.34 (m, 8H), 1.52 (s, 3H), 1.12 (s, 9H), 1.08 - 0.84 (m, 10H), 0.76 - 0.62 (m, 1 H), 0.50 (dd, *J* = 12.6, 6.6 Hz, 1 H).

[0224] Example **30.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-14-methoxy-9-(2-methylpropyl)-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Step 1. Preparation of **30-1:** A mixture of Intermediate **B6** (139 mg, 0.405 mmol), Intermediate **E1** (170 mg, 0.625 mmol), and cesium carbonate (203 mg, 0.623 mmol) in 3.3 mL of acetonitrile was stirred at room temperature under argon overnight. Reaction mixture was filtered over Celite, washing with ethyl acetate, and filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0-30% ethyl acetate in hexanes) to yield **30-1** (170 mg) as a clear film. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{39}ClN_3O_6$: 536.24; found: 536.31.

Step 2. Preparation of **30-2:** A solution of hydrogen chloride in dioxane (4.0 M, 0.16 mL, 0.64 mmol) was added to a solution of **30-1** (168 mg, 0.314 mmol) in 3.3 mL of dioxane at room temperature. After thirty minutes, an additional 4 equivalents of HCl was added and mixture was stirred overnight. An additional 25 equivalents of HCl was then added. After thirty minutes, an additional 19 equivalents of HCl was added. After one hour, an additional 29 equivalents of HCl was added. After thirty minutes, reaction mixture was concentrated under reduced pressure to yield **30-2** (148 mg, 85% purity), which was used in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{31}ClN_3O_4$: 436.19; found: 436.25.

Step 3. Preparation of **30-3:** HATU (144 mg, 0.379 mmol, Oakwood) and DIPEA (0.28 mL, 1.58 mmol) were added to a mixture of **30-2** (148 mg, 0.315 mmol) and Intermediate **D1** (99 mg, 0.348 mmol) in 3.5 mL of DMF under argon. After stirring overnight, reaction mixture was poured into water and extracted with ethyl acetate (3 x). Combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0-50% ethyl acetate in hexanes) to yield **30-3** (136 mg) as a white solid. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{37}H_{54}ClN_4O_7$: 701.36; found: 701.47.

Step 4. Preparation of **30-4:** $Pd(dppf)_2Cl_2$•CH_2Cl_2 (35 mg, 0.043 mmol) was added to a degassed mixture of **30-3** (135 mg, 0.193 mmol), potassium vinyltrifluoroborate (41 mg, 0.306 mmol), and triethylamine (0.040 mL, 0.289 mmol) in 2.1 mL of ethanol at room temperature. Reaction mixture was heated at 78 °C under argon for 45 minutes. After cooling to room temperature, reaction mixture was poured into water and extracted with ethyl acetate (three times). Combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield **30-4** (133 mg), which was used in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{39}H_{57}N_4O_7$: 693.41; found: 693.48.

Step 5. Preparation of **30-5:** A mixture of **30-4** (133 mg, 0.192 mmol) and Zhan 1B catalyst (16 mg, 0.022 mmol, Strem) in 38 mL of DCE was deoxygenated under argon for 25 minutes. The mixture was then heated at 95 °C for 50 minutes. After cooling to room temperature, reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0-50% ethyl acetate in hexanes) to yield **30-5** (70 mg) as a light yellow film. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{37}H_{53}N_4O_7$: 665.38; found: 665.50.

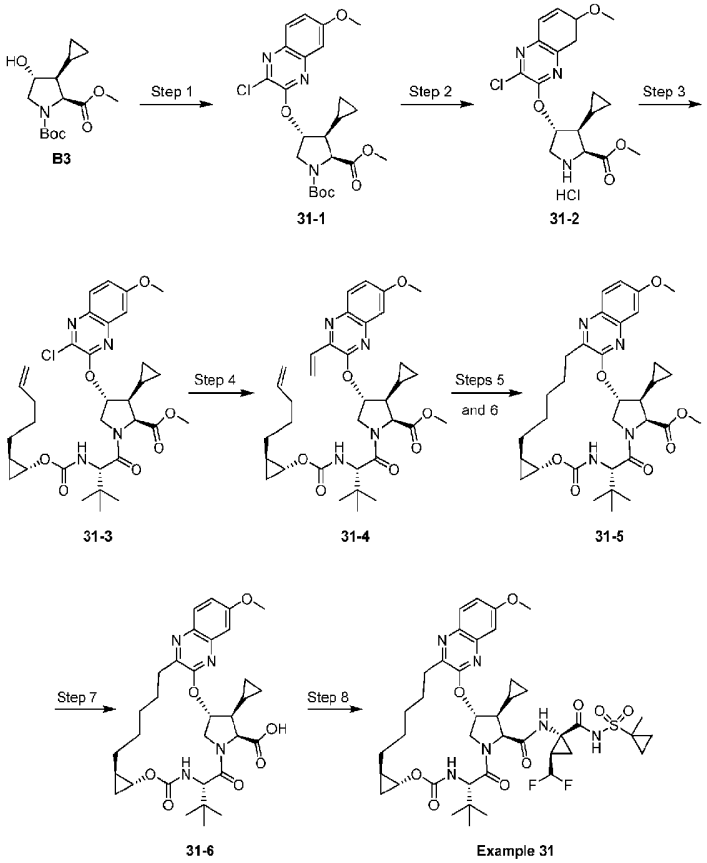
Step 6. Preparation of **30-6:** Palladium on carbon (10 wt % Pd, 22 mg, 0.0208 mmol) was added to a solution of **30-5** (69 mg, 0.104 mmol) in 3 mL of ethanol. Mixture was then stirred under an atmosphere of hydrogen for 1 hour and then was filtered over Celite, washing with ethyl acetate. Filtrate was concentrated under reduced pressure to yield **30-6** (64 mg) as a light yellow-brown solid film, which was used in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{37}H_{55}N_4O_7$: 667.40; found: 667.43.

Step 7. Preparation of **30-7:** TMSOTf (0.050 mL, 0.274 mmol) was added dropwise to a solution of **30-6** (30 mg, 0.045 mmol) in 1.2 mL of dichloromethane under argon at room temperature. After 45 minutes, reaction mixture was concentrated under reduced pressure. The resulting film was taken up in 5 mL of toluene and concentrated under reduced pressure. This process was repeated a second time to yield **30-7** (27 mg), which was used in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{47}N_4O_7$: 611.34; found: 611.41.

Step 8. Preparation of Example **30:** HATU (28 mg, 0.074 mmol, Oakwood) and DIPEA (0.050 mL, 0.281 mmol) were added to a mixture of **30-7** (27 mg, 0.045 mmol) and Intermediate **A10** (22 mg, 0.072 mmol) in 2.2 mL of acetonitrile under argon. After stirring overnight, reaction mixture was poured into water and extracted with ethyl acetate (3 x). Combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0-50% ethyl acetate in hexanes) and reverse phase prep HPLC (15-100% acetonitrile in water, with 0.1% trifluoroacetic acid buffer) to yield the trifluoroacetic acid salt of Example **30** (18 mg) as a light yellow solid, after lyophilization. Analytic HPLC RetTime: 8.96 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{42}H_{59}F_2N_6O_9S$: 861.40; found: 861.30. ^1H NMR (400 MHz, CD_3OD): 5 9.17 (s, 1H), 7.80 (d, J = 8.8 H, 1H), 7.23 (dd, J = 8.8, 2.8 Hz, 1H), 7.14 (d, J = 2.8 Hz, 1 H), 5.81 (td, J_{H-F} = 56 Hz, J = 7.6 Hz, 1 H); 5.77 (d, J = 3.2 Hz, 1 H), 4.55 (d, J = 7.2 Hz, 1 H), 4.39 (t, J = 5.6 Hz, 2H), 4.16 (dd, J = 11.8, 4 Hz, 1 H), 3.91 (s, 3H), 3.79-3.71 (m, 1 H), 2.98-2.90 (m, 1 H), 2.84 (dd, J = 12.6, 4.8 Hz, 1 H), 2.79-2.72 (m, 1 H), 2.06-1.91 (m, 3H), 1.77 (m, 3H), 1.64-1.44 (m, 6H), 1.51 (s, 3H), 1.44-1.32 (m, 3H), 1.15-1.07 (m, 1 H), 1.10 (s, 9H), 1.06-0.96 (m, 3H), 1.04-1.01 (m, 6H), 0.93-0.89 (m, 2H), 0.79-0.68 (m, 1 H), 0.52-0.47 (m, 1 H).

[0225] Example **31.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-9-cyclopropyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-

8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Step 1. Preparation of **31-1:** An unpurified sample of Intermediate **B3** was treated with Intermediate **E1** (217 mg, 0.797 mmol), MeCN (5.7 mL) and Cs_2CO_3 (371 mg, 1.14 mmol). After stirring at rt for 17 h, the reaction mixture was filtered over Celite and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (20% to 40% EtOAc/Hex) to afford quinoxaline **31-1** (143 mg). LCMS-ESI$^+$ (*m/z*): [M-Boc+2H]$^+$calcd for $C_{18}H_{21}ClN_3O_4$: 378.12; found: 378.59.

Step 2. Preparation of **31-2:** Quinoxaline **31-1** (143 mg, 0.299 mmol) was dissolved in DCM (10 mL) and treated with HCl (4.0 M in dioxane, 5 mL, 20.0 mmol). After stirring for 2 h at rt, the reaction mixture was concentrated and the crude **31-2** was carried on without further purification.

Step 3. Preparation of **31-3:** The crude amine hydrochloride **31-2** was treated with BEP (115 mg, 0.419 mmol), Intermediate **D1** (120 mg, 0.423 mmol), EtOAc (9 mL), NMP (1 mL) and DIPEA (0.37 mL, 2.1 mmol), then heated to 50 °C. After 1.5 h, the reaction mixture was diluted with Et_2O. The organic solution was washed successively with saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (15% to 30% EtOAc/Hex) to afford amide **31-3** (166 mg). LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{33}H_{44}ClN_4O_7$: 643.29; found: 643.48.

Step 4. Preparation of **31-4:** Amide **31-3** (166 mg, 0.258 mmol) was treated with potassium vinyltrifluoroborate (52 mg, 0.387 mmol), Pd(dppf)Cl_2•DCM (21 mg, 0.0258 mmol), EtOH (2.6 mL) and TEA (0.054 mL), then heated to reflux. After 50 min, the reaction mixture was diluted with EtOAc and washed with H_2O and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (15% to 40% EtOAc/Hex) to afford vinyl quinoxaline **31-4** (145 mg). LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{35}H_{47}N_4O_7$: 635.34; found: 635.58.

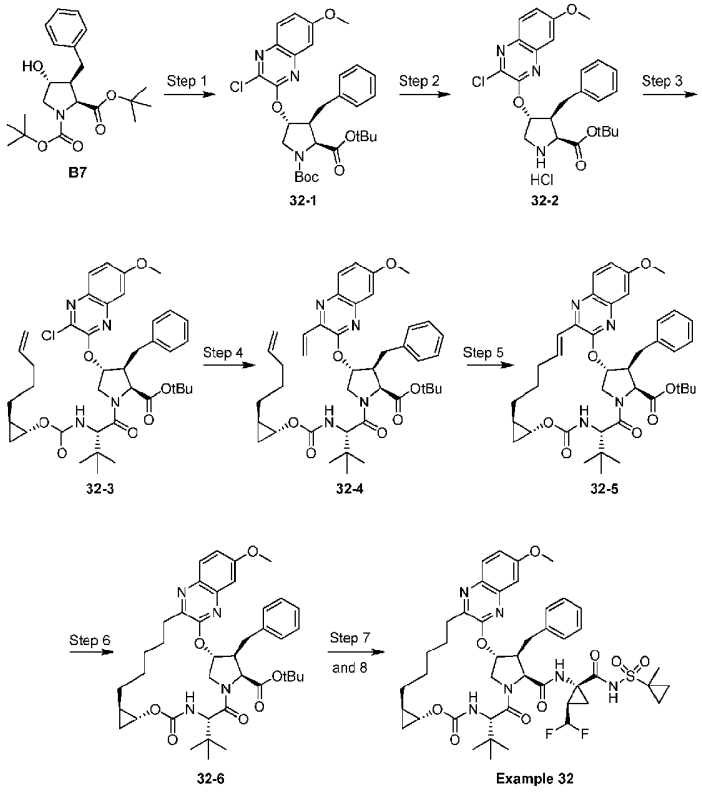
Steps 5 and 6. Preparation of **31-5:** Vinyl quinoxaline **31-4** (145 mg, 0.228 mmol) was suspended in DCE (46 mL) and treated with Zhan 1B catalyst (33 mg, 0.0456 mmol, Strem). The suspension was deoxygenated with bubbling N_2 for 22 min, then heated to reflux for 50 min. The reaction mixture was then filtered over Celite and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (25% to 35% EtOAc/Hex) to afford the desired macrocycle (54 mg; LCMS-ESI$^+$ (*m/z*): [M +H]$^+$ calcd for $C_{33}H_{43}N_4O_7$: 607.31; found: 607.67). The macrocyclic product of step 5 was dissolved in EtOH (10 mL) and

treated with 10% Pd/C (45 mg). Hydrogen from a balloon was bubbled through the suspension for 1 min and hydrogenation (1 atm) was continued for an additional 1.5 h. The reaction mixture was filtered over Celite and concentrated under reduced pressure to afford the desired macrocycle **31-5** which was carried on without further purification. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{33}H_{45}N_4O_7$: 609.33; found: 609.95.

Step 7. Preparation of **31-6:** The crude product **31-5** was dissolved in THF and treated with LiOH (1.0 M in H_2O, 5 mL, 5 mmol). After stirring at rt for 3 d, the reaction mixture was heated to reflux for 20 h. The mixture was then poured into H_2O and acidified to pH ~1-2 with 10% HCl. The aqueous layer was extracted three times with DCM. The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (80% to 100% EtOAc/Hex) to afford carboxylic acid **31-6** (24 mg). LCMS-ESI$^+$ (*m/z*): [M +H]$^+$ calcd for $C_{32}H_{43}N_4O_7$: 595.31; found: 595.12.

Step 8. Preparation of Example **31:** Carboxylic acid **31-6** (24 mg, 0.040 mmol) and Intermediate **A10** (25 mg, 0.081 mmol) were treated with TBTU (23 mg, 0.081 mmol), DMAP (10 mg, 0.081 mmol), DCM (2 mL) and DIPEA (0.070 mL, 0.40 mmol). The reaction mixture was stirred at rt for 15 h then concentrated under reduced pressure. The crude residue was purified by HPLC to afford Example **31** (13 mg, 34%) in approximately 90% purity as a TFA salt. Analytic HPLC RetTime: 8.92 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{41}H_{55}F_2N_6O_9S$: 845.37; found: 845.67. ^{1}H NMR (400 MHz, CD_3OD) δ 9.13 (s, 1 H), 7.79 (d, *J* = 9.1 Hz, 1 H), 7.23 (dd, *J* = 9.1, 2.7 Hz, 1 H), 7.13 (d, *J* = 2.7 Hz, 1 H), 6.05 - 5.65 (m, 2H), 4.55 (d, *J* = 7.0 Hz, 1 H), 4.47 (d, *J* = 11.7 Hz, 2H), 4.27 (dd, *J* = 12.0, 3.7 Hz, 1 H), 3.94 (s, 3H), 3.78 (dd, *J* = 6.8, 2.8 Hz, 1 H), 2.99 - 2.86 (m, 1 H), 2.80 (td, *J* = 13.2, 4.1 Hz, 1 H), 1.98 (d, *J* = 28.8 Hz, 2H), 1.92 - 1.67 (m, 4H), 1.65 - 1.41 (m, 10H), 1.33 (d, *J* = 27.7 Hz, 3H), 1.20 - 1.06 (m, 9H), 1.04 - 0.84 (m, 6H), 0.82 - 0.62 (m, 3H), 0.61 - 0.41 (m, 2H), 0.06 (dd, *J* = 9.2, 4.9 Hz, 1 H).

[0226] Example **32.** Preparation of (1aR,5S,8S,9S,10R,22aR)-9-benzyl-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Step 1. Preparation of **32-1:** To a solution of Intermediate **B7** (390 mg, 1.00 mmol) and Intermediate **E1** (272 mg, 1.00 mmol) in MeCN (5 mL) was added cesium carbonate (390 mg, 1.00 mmol) at rt under an argon atmosphere. After 24 h, the reaction mixture was diluted with ethyl acetate (50 mL). The resulting mixture was washed with saturated aqueous sodium bicarbonate solution (50 mL) and brine (50 mL), was dried over anhydrous sodium sulfate, and was concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford quinoxaline **32-1** (550 mg) as a

colorless oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{37}ClN_3O_6$: 570.2; found: 570.2.

Step 2. Preparation of **32-2:** To a solution of **32-1** (549 mg, 0.96 mmol) in dioxane (2 mL) was added 4 M hydrochloric acid in dioxane (2 mL, 1 mmol) and the reaction was stirred at rt. After 24 h, the reaction mixture was concentrated *in vacuo* to afford amine hydrochloride **32-2** (461 mg) as an off white solid, which was used directly in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{29}ClN_3O_4$: 470.2; found: 470.2.

Step 3. Preparation of **32-3:** To a solution of **32-2** (461 mg, 0.96 mmol) and Intermediate **D1** (369 mg, 1.10 mmol) in MeCN (5 mL) was added HATU (418 mg, 1.10 mmol) followed by DIPEA (869 µL, 5.00 mmol) at rt under and argon atmosphere. After 24 h, the reaction mixture was concentrated *in vacuo,* and the crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford **32-3** (202.6 mg) as a colorless oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{40}H_{52}ClN_4O_7$: 735.3; found: 735.4.

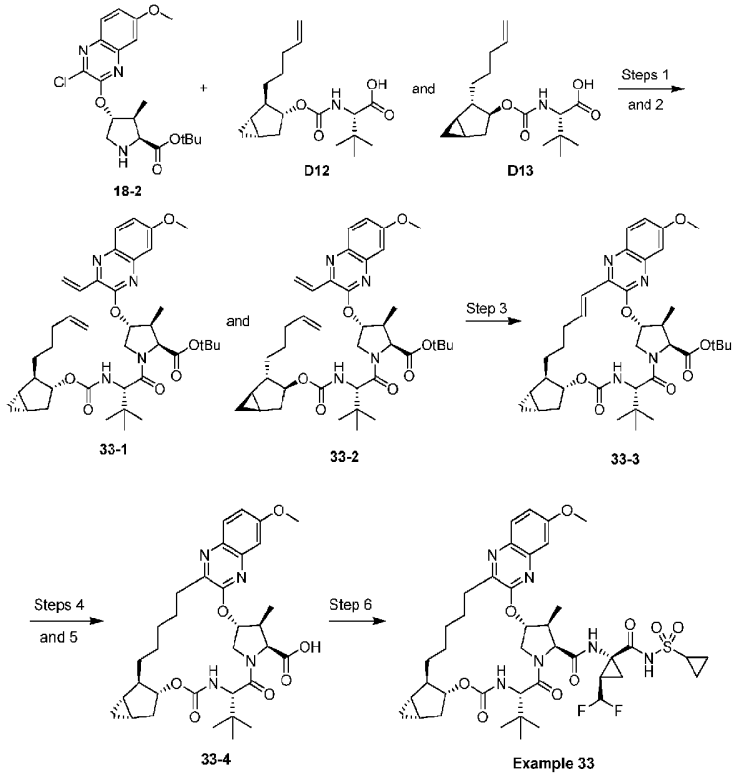
Step 4. Preparation of **32-4:** To a solution of **32-3** (202 mg, 276 µmol), TEA (56 µL, 414 µmol) and potassium vinyltrifluoroborate (56 mg, 414 µmol) in EtOH (2.76 mL) was added $PdCl_2$(dppf) (22.5 mg, 27.6 µmol). The reaction mixture was degassed with argon for 10 min and was heated to 78 °C. After 1 h, the reaction mixture was allowed to cool to rt and was concentrated *in vacuo.* The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford **32-4** (163 mg) as a yellow oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{42}H_{55}N_4O_7$: 727.4; found: 727.5.

Step 5. Preparation of **32-5:** To a solution of **32-4** (163 mg, 220 µmol) in DCE (44 mL) was added Zhan 1B catalyst (16 mg, 22 µmol, Strem) and the reaction mixture was degassed for 10 minutes with argon. The reaction mixture was then heated to 100 °C. After 45 min, the reaction mixture was allowed to cool to rt and was concentrated *in vacuo.* The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford **32-5** (125 mg) as a light yellow oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{40}H_{51}N_4O_7$: 699.4; found: 699.4.

Step 6. Preparation of **32-6:** To a solution of macrocycle **32-5** (124 mg, 178 µmol) in ethanol (890 µL) was added Pd/C (10 wt % Pd, 19 mg, 18 µmol) at rt under an argon atmosphere. The reaction vessel was evacuated and refilled with hydrogen gas (3 ×) and the reaction mixture was stirred vigorously at rt under 1 atm H_2. After 2.5 h, the reaction mixture was diluted with ethyl acetate (5 mL) and was filtered through a pad of Celite with ethyl acetate washings (3 × 5 mL). The filtrate was concentrated *in vacuo* to afford **32-6** (139 mg), which was used directly in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{40}H_{53}N_4O_7$: 701.4; found: 701.5.

Steps 7 and 8. Preparation of Example **32:** To a solution of **32-6** (124 mg, 178 µmol) in DCM (3 mL) was added TFA (2 mL) at rt under an argon atmosphere. After 3 h, the reaction mixture was concentrated *in vacuo* and was azeotropically dried from toluene (2 × 2 mL) to afford the desired carboxylic acid as a yellow oil, which was used directly in the next step without further purification. (126 mg; LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{36}H_{45}N_4O_7$: 645.3; found: 645.4). To a solution of this carboxylic acid (120 mg, 178 µmol) and Intermediate **A10** (119 mg, 392 µmol) in MeCN (1 mL) was added HATU (151 mg, 392 µmol) followed by DIPEA (155 µL, 890 µmol) at rt under an argon atmosphere. After 30 min, the reaction mixture was concentrated *in vacuo,* and the crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient). The fractions containing the desired product were combined, were repurified by preparatory HPLC (Gemini 5u C18 110A column, 5-100% MeCN/H_2O, 0.1% trifluoroacetic acid modifier) and were lyophilized to afford the TFA salt of Example **32** (23 mg) as a white powder. Analytic HPLC RetTime: 8.81 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{45}H_{57}F_2N_6O_9S$: 895.4; found: 895.6. ^{1}H NMR (400 MHz, CD_3OD) δ 9.24 (s, 1 H), 7.73 (d, *J* = 9.1 Hz, 1 H), 7.47 - 7.27 (m, 4H), 7.21 - 7.12 (m, 1 H), 6.65 *(d, J* = 2.9 Hz, 1H), 5.83 (td, J_{H-F} = 55 Hz, *J* = 7.2 Hz, 1 H), 5.77 (br s, 1 H), 4.63 (d, *J* = 6.9 Hz, 2H), 4.50 - 4.28 (m, 3H), 3.93 (s, 2H), 3.79 - 3.71 (m, 1 H), 3.11 - 2.99 (m, 1 H), 2.97 - 2.85 (m, 1 H), 2.82 - 2.61 (m, 3H), 1.92 (br s, 2H), 1.82 - 1.70 (m, 2H), 1.63 - 1.44 (m, 4H), 1.52 (s, 3H), 1.15 (s, 9H), 1.04 (br s, 2H), 1.02 - 0.96 (m, 2H), 0.95 - 0.88 (m, 4H), 0.78 - 0.66 (m, 1 H), 0.56 - 0.46 (m, 1 H).

[0227] Example **33.** Preparation of (1aS,2aR,6S,9S,10S,11R,23aR,23bS)-6-tert-butyl-N-[(1S,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-15-methoxy-10-methyl-4,7-dioxo-1a,2,2a,4,5,6,7,10,11,19,20,21,22,23,23a,23b-hexadecahydro-1H,9H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19][1,10,3,6]dioxadiazacyclononade cino[11,12-b]quinoxaline-9-carboxamide.



Steps 1 and 2. Preparation of diastereomeric mixture **33-1** and **33-2:** Quinoxaline **18-2** (220 mg, 0.56 mmol) was dissolved along with 1:1 diastereomer Intermediate mixture **D12** and **D13** (208 mg, 0.643 mmol) in MeCN (5 mL). DIPEA (280 µL, 1.6 mmol) and HATU (360 mg, 0.95 mmol) were added, and the reaction was stirred for 1.25 h at rt. The reaction was then diluted with EtOAc (30 mL), saturated aqueous $NaHCO_3$ (15 mL), H_2O (10 mL), and brine (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to a crude residue that was dissolved in CH_2Cl_2 and adsorbed onto silica gel (5 g). Purification by silica gel chromatography (10% to 30% EtOAc in hexanes) provided a white foam (352 mg; LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{37}H_{52}ClN_4O_7$: 699.4; found: 699.1). A stirred heterogeneous mixture of this residue, $PdCl_2(dppf)\bullet CH_2Cl_2$ (30.7 mg, 0.0376 mmol) and potassium vinyltrifluoroborate (135 mg, 1.01 mmol) in EtOH (5 mL) was sparged with argon for several minutes. Triethylamine (160 µL, 1.1 mmol) was added and the mixture was heated to 75 °C for 1 h. The reaction mixture was cooled to ambient temperature and was diluted with EtOAc (30 mL), H_2O (15 mL) and brine (15 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (30 mL). The organics were dried over anhydrous Na_2SO_4, filtered and concentrated to afford a crude residue that was dissolved in CH_2Cl_2 and adsorbed onto silica gel (3 g). Purification by silica gel chromatography (10% to 40% EtOAc in hexanes) produced inseparable mixture of **33-1** and **33-2** as a yellow residue (258 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{39}H_{55}N_4O_7$: 691.4; found: 691.7.

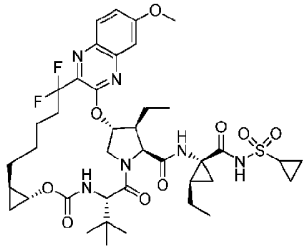
Step 3: Preparation of **33-3:** Diastereomeric mixture **33-1** and **33-2** (258 mg, 0.373 mmol) was dissolved in DCE (125 mL) and the solution was sparged with Ar for 10 min. Zhan 1B catalyst (41 mg, 0.056 mmol, Strem) was added as a solution in DCE (3.3 mL) and the resulting solution was stirred at 85 °C under Ar for 105 min. The reaction mixture was then concentrated onto 5 g silica gel and was purified by silica gel chromatography (0% to 25% EtOAc in hexanes) to afford macrocycle **33-3** as an amorphous residue (81.9 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{37}H_{51}N_4O_7$: 663.4; found: 663.3.

Steps 4 and 5: Preparation of **33-4:** To a solution of **33-3** (81.9 mg, 0.124 mmol) in 1:1 EtOAc:EtOH (4 mL) was added Pd/C (10 wt % Pd, 19 mg). The reaction vessel was purged twice with H_2 and was stirred at rt under 1 atm H_2 for 2.5 h. The reaction mixture was filtered through a pad of Celite and concentrated to afford a crude residue. This residue was dissolved in CH_2Cl_2 (1.2 mL) and TMSOTf (90 µL, 0.50 mmol) was added. The mixture was stirred at rt for 4.5 h. The reaction was then concentrated *in vacuo* and dissolved in CH_2Cl_2 (5 mL). 0.2 M aqueous NaOH (5 mL) was added and the biphasic mixture was stirred at rt for 5 min. The mixture was then acidified with 1 M aqueous HCl (20 mL) and was diluted with CH_2Cl_2 (20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated to afford **33-4** as a crude residue (76.1 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{45}N_4O_7$: 609.3;

found: 608.9.

Step 6: Preparation of Example **33:** To a suspension of acid **33-4** (43 mg, 0.072 mmol) and Intermediate **A9** (40.9 mg, 0.14 mmol) in MeCN (800 µL) was added DIPEA (100 µL, 0.57 mmol). HATU (37 mg, 0.097 mmol) was added to the resulting solution, and the reaction was stirred at rt for 15 h. The reaction was then diluted with EtOAc (20 mL), 0.2 M aqueous HCl (10 mL) and brine (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue. This residue was dissolved in CH_2Cl_2 and was concentrated onto 2 g silica gel. Purification by silica gel chromatography (15% to 55% acetone in hexanes) provided an amorphous residue that was lyophilized from water and MeCN to provide Example **33** as a white amorphous solid (29.6 mg). Analytic HPLC RetTime: 9.07 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_4H_{55}F_2N_6O_9S$: 845.4; found: 845.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1 H), 7.82 (d, *J* = 9.1 Hz, 1 H), 7.19 (dd, *J* = 9.1, 2.7 Hz, 1 H), 7.09 (d, *J* = 2.7 Hz, 1 H), 6.79 (s, 1 H), 6.21 - 5.76 (m, 1 H), 5.65 (d, *J* = 3.9 Hz, 1 H), 5.29 (d, *J* = 9.7 Hz, 1 H), 4.99 (d, *J* = 7.5 Hz, 1 H), 4.47 - 4.29 (m, 4H), 4.16 - 4.09 (m, 1 H), 3.93 (s, 3H), 2.99 - 2.85 (m, 2H), 2.80 - 2.64 (m, 2H), 2.24 - 2.16 (m, 1 H), 2.13 - 2.05 (m, 1 H), 2.01 - 0.95 (m, 29H), 0.56 - 0.45 (m, 1 H), 0.45 - 0.35 (m, 1 H).

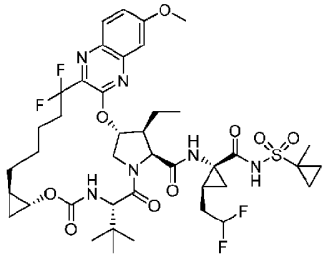
[0228] Example **34.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-{(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethylcyclopropyl}-9-ethyl-18,18-difluoro-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 34

[0229] Example **34** was prepared in a similar fashion to Example **17,** substituting Intermediate **A3** for Intermediate **A10** in Step 7. Example **34** was isolated (5.7 mg) in approximately 95% purity. Analytic HPLC RetTime: 8.81 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{40}H_{55}F_2N_6O_9S$: 833.4; found: 833.25. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.027 (br s, 1 H), 7.98 (d, J = 8.8 Hz, 1 H), 7.29 (dd, J = 9.2, 2.8 Hz, 1 H), 7.09 (d, J = 2.8 Hz, 1 H), 6.32 (br s, 1 H), 5.92 (d, J = 3.6 Hz, 1 H), 5.30 (d, J = 10.0 Hz, 1 H), 4.42 - 4.33 (m, 3H), 4.08 (dd, J = 11.6, 4.0 Hz, 1 H), 3.96 (s, 3H), 3.65 (m, 1 H), 2.93 (m, 1 H), 2.51 (m, 2H), 2.02 (m, 1 H), 1.86 - 1.40 (m, 11 H) 1.34 - 1.14 (m, 7H), 1.09 (s, 9H), 1.10 - 0.82 (m, 6H), 0.72 (m, 1 H), 0.48 (m, 1 H).

[0230] Example **35.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2S)-2-(2,2-difluoroethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-18,18-difluoro-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.

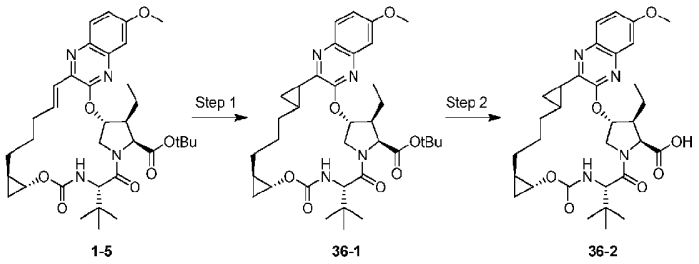


Example 35

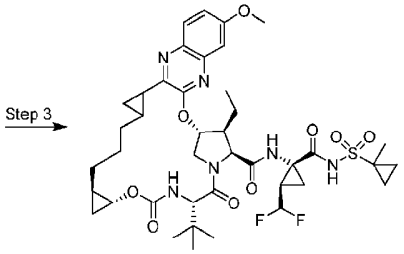
[0231] Example **35** was prepared in a similar fashion to Example **17,** substituting Intermediate **A8** for Intermediate **A10** in Step 7. Example **35** was isolated (12.8 mg) in approximately 90% purity. Analytic HPLC RetTime: 8.78 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{41}H_{55}F_4N_6O_9S$: 883.4; found: 883.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (br s, 1 H), 7.98 (d, J = 9.2 Hz, 1 H), 7.29 (dd, J = 9.2,

2.8 Hz, 1 H), 7.09 (d, J = 2.8 Hz, 1 H), 6.53 (br s, 1 H), 5.91 (d, J = 4.0 Hz, 1 H), 5.84 (tt, J_{H-F} = 56 Hz, J = 3.6 Hz, 1 H), 5.33 (d, J = 6.4 Hz, 1 H), 4.43 (m, 2H), 4.34 (ap d, J = 9.6 Hz, 1 H), 4.08 (dd, J = 11.6, 4.0 Hz, 1 H), 3.96 (s, 3H), 3.99 - 3.94 (m, 1 H), 3.68 (m, 1 H), 2.58 - 2.52 (m, 3H), 2.20 (m, 2H), 1.82 - 1.58 (m, 7H) 1.54 - 1.40 (m, 5H), 1.36 - 1.18 (m, 6H), 1.09 (s, 9H), 1.10 - 1.00 (m, 1 H), 0.85 (m, 2H), 0.69 (m, 1H), 0.49 (m, 1 H).

[0232] Example **36.** Preparation of (1aR,5S,8S,9S,10R,21aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-14-methoxy-3,6-dioxo-1a,3,4,5,6,9,10,17b,18,18a,19,20,21,21a-tetradecahydro-1H,8H-7,10-methanodicyclopropa[13,14:18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



1-5 **36-1** **36-2**



Example 36

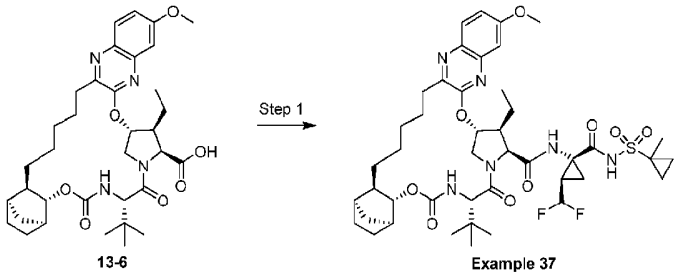
Step 1. Preparation of **36-1:** To a solution of trimethylsulfoxonium iodide (72 mg, 0.32 mmol) in DMSO/THF (1:1, 2 mL) was added sodium hydride (60%, 12 mg, 0.32 mmol) and stirred at rt for 2 h. Macrocycle **1-5** (103 mg, 0.16 mmol) was added dropwise in THF (3 mL). The mixture was heated to 65 °C and stirred for 16 h. After cooling to rt, the mixture was diluted with EtOAc/H_2O, extracted with EtOAc, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-25% EtOAc/hexanes) to give **36-1** (27 mg) as a residue. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{51}N_4O_7$: 651.38; found: 651.52.

Step 2. Preparation of **36-2:** To a solution of **36-1** (26 mg, 0.04 mmol) in DCM (1 mL) was added TMSOTf (0.036 mL, 0.2 mmol) and stirred at rt for 2 h. The reaction was pipetted into stirring 1 N NaOH (2 mL). After 10 min, the mixture was diluted with DCM and acidified to pH 3 with 1 N aqueous HCl. Following extraction of the aqueous layer with DCM, the combined organics were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-10% EtOAc/MeOH) to give **36-2** (24 mg) as a residue that was used without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{43}N_4O_7$: 595.31; found: 595.43.

Step 3. Preparation of Example **36:** To a solution of **36-2** (24 mg, 0.041 mmol), Intermediate **A10** (16 mg, 0.053 mmol), TBTU (19 mg, 0.06 mmol) and DMAP (8 mg, 0.06 mmol) in DCM (2 mL) was added DIPEA (0.021 mL, 0.12 mmol) and the reaction was stirred at rt for 16 h. Additional Intermediate A10 (16 mg, 0.053 mmol), TBTU (19 mg, 0.06 mmol), DMAP (8 mg, 0.06 mmol), and DIPEA (0.021 mL, 0.12 mmol) were added and the reaction was stirred at rt for 4 h. The reaction was quenched with water, diluted with EtOAc, washed with sat. aqueous $NaHCO_3$, brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by reverse phase HPLC (Gemini, 45-85% MeCN/H_2O + 0.1% TFA) and lyophilized to give Example **36** (3 mg) as a TFA salt. Analytic HPLC RetTime: 9.06 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{41}H_{55}F_2N_6O_9S$: 845.37; found: 845.43. ^1H NMR (400 MHz, CD_3OD) δ 9.31 (s, 1 H), 7.72 (d, J = 10 Hz, 1 H), 7.20 - 7.17 (m, 2H), 5.60 - 5.82 (m, 2H), 5.51 (s, 1 H), 4.72 (d, J = 7.2 Hz, 1 H), 4.43 (d, J = 11.6 Hz, 1 H), 4.31 (s, 1 H), 4.26 - 4.22 (dd, J = 11.6, 4 Hz , 1 H), 3.94 (s, 3H), 3.78 (m, 1 H),2.60 (m, 1 H), 2.27 (m, 1 H), 2.04 (s, 3H), 1.68 (m, 3H), 1.59 (m, 2H), 1.54 - 1.15 (m, 11 H), 1.09 (s, 9H), 0.95 - 0.86 (m, 8H), 0.47 (m, 1 H).

[0233] Example **37.** Preparation of (1R,4S,4aR,8S,11S,12S,13R,25aR)-8-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-

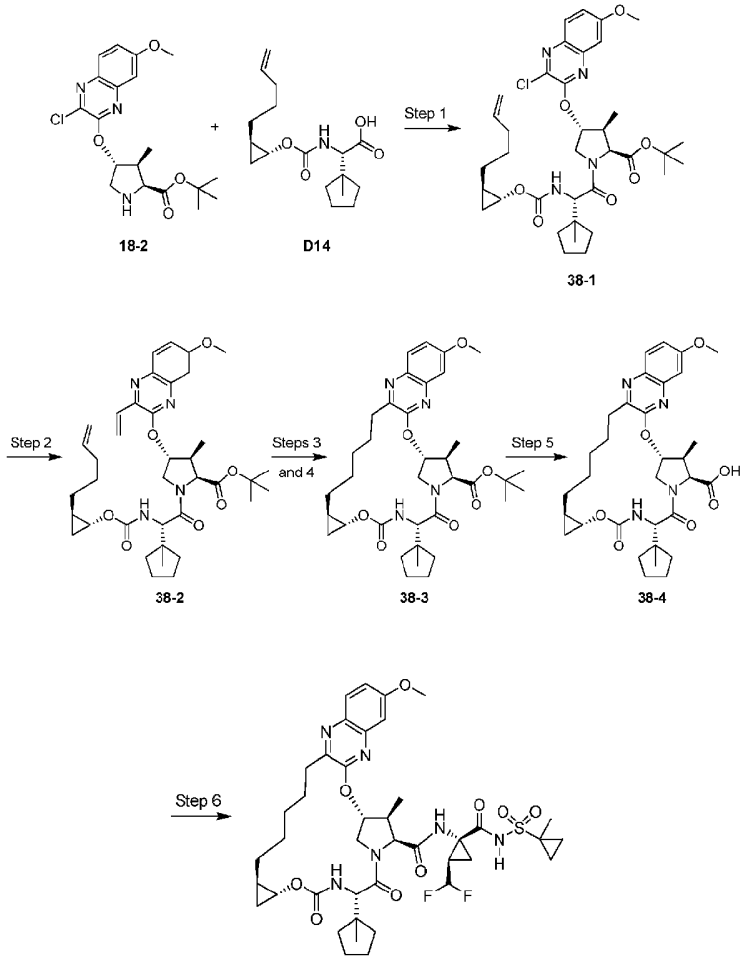
methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-12-ethyl-17-methoxy-6,9-dioxo-2,3,4,4a,6,7,8,9,12,13,21,22,23,24,25,25a-hexadecahydro-1H,11H-1,4:10,13-dimethanoquinoxalino[2,3-k][1,10,3,6]benzodioxadiazacyclononadecine-11-carboxamide.



13-6 Example 37

[0234] Step 1. Preparation of Example **37:** To a solution of **13-6** (76 mg, 0.12 mmol), Intermediate **A10** (44 mg, 0.14 mmol), HATU (55 mg, 0.14 mmol) and DMAP (21 mg, 0.18 mmol) in DMF (2 mL) was added DIPEA (0.11 mL, 0.6 mmol) and the reaction was stirred at rt for 16 h. Additional Intermediate **A10** (44 mg, 0.14 mmol), HATU (55 mg, 0.14 mmol), DMAP (21 mg, 0.18 mmol), followed by DIPEA (0.11 mL, 0.6 mmol) was added and the reaction was stirred at 40 °C for 50 h. The reaction was quenched with water, diluted with EtOAc, washed with sat. aqueous $NaHCO_3$, brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by reverse phase HPLC (Gemini, 45-85% MeCN/H_2O + 0.1% TFA) and lyophilized to give Example **37** (30 mg) as a TFA salt. Analytic HPLC RetTime: 9.44 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{44}H_{61}F_2N_6O_9S$: 887.42; found: 887.50. ^1H NMR (400 MHz, CD_3OD) δ 9.24 (s, 1 H), 7.76 (d, J = 9.2 Hz, 1 H), 7.20 (dd, J = 8.8, 2.4 Hz, 1 H), 7.12 (m, 1 H), 5.95 - 5.66 (m, 2H), 5.43 (s, 1 H), 4.51 (d, J = 7.6 Hz, 1 H), 4.41 (s, 1 H), 4.20 - 4.10 (m, 2H), 3.88 (s, 3H), 2.94 - 2.88 (m, 1 H), 2.73 - 2.63 (m, 2H), 2.11 (br, 2H), 2.02 - 0.83 (m, 41 H).

[0235] Example **38.** Preparation of (1aR,5S,8S,9S,10R,22aR)-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-14-methoxy-9-methyl-5-(1-methylcyclopentyl)-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide



Example 38

Step 1. Preparation of **38-1:** Amine **18-2** (192 mg, 0.487 mmol) was treated with BEP (246 mg, 0.898 mmol), Intermediate **D14** (278 mg, 0.898 mmol), EtOAc (9 mL), NMP (1 mL) and DIPEA (0.42 mL, 2.4 mmol), then heated to 50 °C. After 1 h, the reaction mixture was diluted with EtOAc. The organic solution was washed successively with sat. aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (15% to 35% EtOAc/Hex) to afford amide **38-1** (264 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{36}H_{50}ClN_4O_7$: 685.34; found: 685.82.

Step 2. Preparation of **38-2:** Amide **38-1** (264 mg, 0.385 mmol) was treated with potassium vinyltrifluoroborate (82 mg, 0.615 mmol), Pd(dppf)Cl_2•DCM (33 mg, 0.041 mmol), EtOH (4.0 mL) and TEA (0.086 mL, 0.62 mmol), then heated to reflux. After 55 min, the reaction mixture was diluted with EtOAc and washed with H_2O and brine. The organics were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (15% to 30% EtOAc/Hex) to afford vinyl quinoxaline **38-2** (168 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{38}H_{53}N_4O_7$: 677.39; found: 677.38.

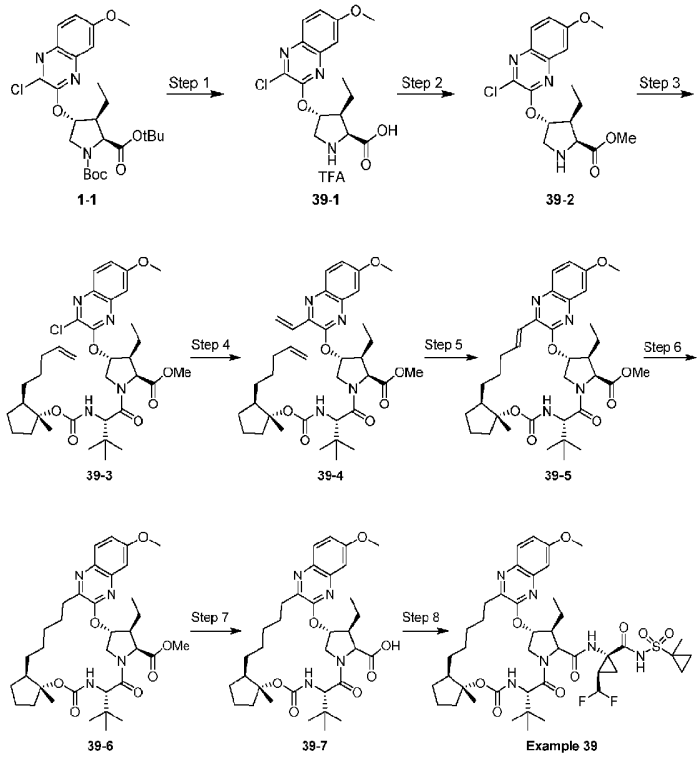
Steps 3 and 4. Preparation of **38-3:** Vinyl quinoxaline **38-2** (225 mg, 0.332 mmol) was suspended in DCE (66 mL) and treated with Zhan 1 B catalyst (42 mg, 0.067 mmol, Strem). The suspension was degassed with bubbling N_2 for 28 min, then heated to reflux for 90 min. The reaction mixture was then filtered over Celite and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (15% to 30% EtOAc/Hex) to afford the desired macrocycle (168 mg; LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{36}H_{49}N_4O_7$: 649.36; found: 649.33). The macrocycle was dissolved in EtOH (25 mL) and EtOAc (5 mL) and treated with Pd/C (10 wt% Pd, 95 mg). Hydrogen from a balloon was bubbled through the suspension for 1 min the reaction was stirred under an H_2 atmosphere for an additional 1.5 h. Upon completion, the reaction mixture was filtered over Celite and concentrated *in vacuo* to afford the desired macrocycle **38-3** which was carried on without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{36}H_{51}N_4O_7$: 651.38; found: 651.42.

Step 5. Preparation of **38-4:** Unpurified **38-3** from the previous step was dissolved in DCM (10 mL) and treated with TMSOTf (0.23

mL, 1.3 mmol). After stirring at rt for 1 h 15 min, the reaction mixture was concentrated *in vacuo*. The residue was redissolved in DCM and pipetted into 1 M aqueous NaOH. The mixture was agitated for 1 min, then acidified to pH ~ 1-2 with 10% aqueous HCl. The aqueous layer was extracted three times with DCM and combined organics dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (0% to 20% MeOH/EtOAc) to afford carboxylic acid **38-4** (131 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{32}H_{43}N_4O_7$: 595.31; found: 595.29.

Step 6. Preparation of Example **38:** Carboxylic acid **38-4** (131 mg, 0.220 mmol) and Intermediate **A10** (81 mg, 0.264 mmol) were treated with TBTU (85 mg, 0.264 mmol), DMAP (32 mg, 0.264 mmol), DCM (2.6 mL) and DIPEA (0.38 mL, 2.2 mmol). The reaction mixture was stirred at rt for 14 h, then concentrated under reduced pressure. The crude residue was purified by HPLC to afford Example **38** (74 mg) in approximately 90% purity as a TFA salt. Analytic HPLC RetTime: 8.93 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{41}H_{55}F_2N_6O_6S$: 845.37; found: 845.57. ^{1}H NMR (400 MHz, CD_3OD) δ 9.12 (s, 1 H), 7.77 (d, *J* = 9.2 Hz, 1 H), 7.20 (dd, *J* = 9.0 Hz, 2.7 Hz, 1 H), 7.16 (d, *J* = 2.8 Hz, 1 H), 5.81 (td, *J* = 55.9, 6.6 Hz, 1 H), 5.59 (d, *J* = 3.5 Hz, 1 H), 4.52 (d, *J* = 6.8 Hz, 1 H), 4.50 (s, 1 H), 4.40 (*d,J*=12.0Hz, 1H),4.18(dd, *J* = 11.9Hz,3.9Hz, 1 H), 3.93 (s, 3H), 3.74 (m, 1 H), 2.97-2.90 (m, 1 H), 2.85-2.75 (m, 2H), 2.01 (m, 2H), 1.85-1.41 (m, 21 H), 1.12 (s, 3H), 1.08 (d, *J* = 7.4 Hz, 3H), 0.96 (m, 2H), 0.91 (t, *J* = 4.3 Hz, 2H), 0.70 (m, 1H), 0.48 (m, 1 H).

[0236] Example **39.** Preparation of (3aR,7S,10S,11S,12R,24aR)-7-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-11-ethyl-16-methoxy-3a methyl-5,8-dioxo-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10H-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide.



Step 1. Preparation of **39-1:** Quinoxaline ether **1-1** (588.7 mg, 1.159 mmol) was dissolved in TFA (5 mL). The solution was stirred at room temperature for 3 h. The TFA was removed *in vacuo* to give the TFA salt of **39-1** (631.2 mg) as a colorless powder. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{19}ClN_3O_4$: 352.1; found: 352.1.

Step 2. Preparation of **39-2:** The TFA salt of **39-1** (631.2 mg, 1.159 mmol) was dissolved in CH_2Cl_2/MeOH (3 mL/3 mL). To the solution was added a solution of $TMSCHN_2$ (2 M hexane, 3 mL, 5.177 mmol) at rt. The solution was stirred for 30 min to produce a suspension that was filtered through a fritted glass funnel to remove solids. The filtrate was concentrated *in vacuo* to afford a residue that was purified by silica gel chromatography (100% ethyl acetate) to produce methyl ester **39-2** (213.0 mg) as colorless crystals. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{21}ClN_3O_4$: 366.1; found: 366.1.

Step 3. Preparation of **39-3:** Intermediate **D7** (191.2 mg, 0.587 mmol) and methyl ester **39-2** (414.1 mg, 1.132 mmol) were treated with HATU (860.0 mg, 2.264 mmol) and DIPEA (0.59 mL, 3.396 mmol) in DMF (8 mL) at rt for 4 h. The reaction was quenched with H_2O (50 mL) and extracted with EtOAc (50 mL three times). The combined organics were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After removal of drying agent by filtration, the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (20% ethyl acetate in hexanes) to give the desired amide **39-3** (573.9 mg) as colorless oil. LCMS-ESI$^+$ (*m/z*): $[M+Na]^+$ calcd for $C_{33}H_{49}ClN_4NaO_7$: 695.3; found: 695.3.

Step 4. Preparation of **39-4:** Amide **39-3** (573.9 mg, 0.8524 mmol), potassium trifluorovinylborate (171.3 mg, 1.279 mmol) and $PdCl_2dppf•CH_2Cl_2$ (62.4 mg, 0.085 mmol) were treated with Et_3N (0.18 mL, 1.279 mmol) in EtOH (8 mL) under a nitrogen atmosphere and gently refluxed for 30 min. The reaction was diluted with PhMe (30 mL) and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (20% ethyl acetate in hexanes) to give the desired vinyl quinoxaline **39-4** (542.0 mg, 0.8152 mmol) as an orange foam. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{37}H_{52}N_4NaO_7$: 687.4; found: 687.3.

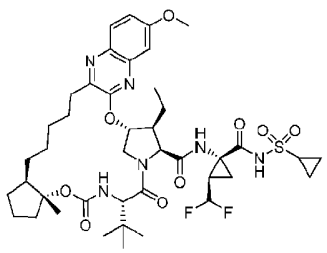
Step 5. Preparation of **39-5:** The vinyl quinoxaline **39-4** (542.0 mg, 0.8152 mmol) was treated with Zhan 1 b catalyst (59.8 mg, 0.08 mmol, Strem) in DCE (41 mL). The mixture was heated at 80°C for 1 h. Additional Zhan 1 b catalyst (59.8 mg, 0.08 mmol, Strem) was added and the mixture to heat at 80 °C for an additional 30 min. The solvent was removed *in vacuo* and the residue purified by silica gel chromatography (20% ethyl acetate in hexanes) to produce macrocycle **39-5** (401.0 mg, 0.6297 mmol) as an orange oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{35}H_{49}N_4O_7$: 637.4; found: 637.3.

Step 6. Preparation of **39-6:** Macrocycle **39-5** (401.0 mg, 0.6297 mmol) was taken up in 1,4-dioxane (15 mL) and treated with Pd/C (10% wt Pd, 200.0 mg) and MgO (200.0 mg) stirred under an atmosphere of hydrogen. The mixture was stirred at rt for 1 h. The reaction mixture was filtered through Celite (5 g) using EtOAc (80 mL). The solvent was removed *in vacuo* to give macrocycle **39-6** (425.3 mg) as a pale orange oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{35}H_{51}N_4O_7$: 639.4; found: 639.3.

Step 7. Preparation of **39-7:** Macrocycle **39-6** (74.8 mg, 0.110 mmol) was treated with 2 M aqueous LiOH aqueous solution (1.6 mL, 3.15 mmol) in MeOH/THF (4 mL /4 mL) at rt for 8 h, 50 °C for 2 h and then 60 °C for 3 h. The mixture was cooled to 0 °C using ice-water bath. To the mixture was added brine (30 mL). The whole was extracted with CH_2Cl_2 (30 mL three times). The organic layer was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. After removal of the drying agent by filtration, the solvent was removed *in vacuo* to give carboxylic acid **39-7** (370.6 mg, 0.5932 mmol) as a colorless oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{49}N_4O_7$: 625.4; found: 625.3.

Step 8. Preparation of Example **39:** Carboxylic acid **39-7** (100.0 mg, 0.1601 mmol) and Intermediate **A10** (73.2 mg, 0.2401 mmol) were treated with HATU (91.3 mg, 0.2401 mmol) and DIPEA (0.14 mL, 0.8005 mmol) in DMF (3 mL) at rt for 5 h. The reaction was quenched with H_2O (30 mL) and extracted with EtOAc (30 mL three times). The organic layer was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. After removal of the drying agent by filtration, the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (25 to 100% ethyl acetate in hexanes). Fractions containing desired product were concentrated *in vacuo* and the residue further purified by super critical fluid column chromatography (DAICEL Chiralpak IC 10x250 mm, 18.9 mL/min, 35% MeOH, 15 atm, 40 °C) to give Example **39** (80.5 mg, 0.0920 mmol, 57%) as a colorless powder. Analytic HPLC RetTime: 9.35 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{43}H_{61}F_2N_6O_9S$: 875.4; found: 875.4. ^{1}H NMR (300 MHz, CD_3OD) δ 7.81 (d, *J* = 9.6 Hz, 1 H), 7.27 (s, 1 H), 7.24 (d, *J* = 9.6 Hz, 1 H), 6.68 (d, *J* = 9.6 Hz, 1 H), 5.74-6.30 (m, 3H), 4.73 (d, *J* = 7.2 Hz, 1 H), 4.73 (d, J = 7.2 Hz, 1 H), 4.40-4.60 (m, 1 H), 4.22 (d, *J* = 9.6 Hz, 1 H), 3.95 (s, 3H), 3.61 (q, *J* = 7.2 Hz, 2H), 3.16-3.30 (m, 1 H), 2.50-2.77 (m, 2H), 2.20-0.60 (m, 21 H), 1.35 (s, 3H) 1.12 (t, *J* = 7.2 Hz, 3H), 1.18 (s, 3H), 1.02 (s, 9H).

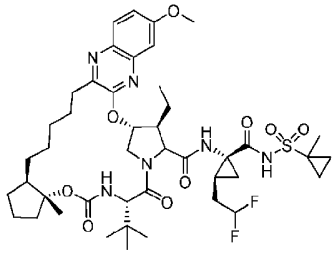
[0237] Example **40.** Preparation of (3aR,7S,10S,11S,12R,24aR)-7-tert-butyl-N-[(1 R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-11-ethyl-16-methoxy-3a-methyl-5,8-d ioxo-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10H-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide



Example 40

[0238] Example **40** was prepared in a similar fashion to Example 39, substituting Intermediate **A9** for Intermediate **A10** in Step 8. Example **40** was isolated (70.9 mg) in approximately 92% purity. Analytic HPLC RetTime: 9.24 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{42}H_{59}F_2N_6O_9S$: 861.4; found: 861.4. ^{1}H NMR (300 MHz, CD_3OD) δ 7.80 (d, *J* = 9.6 Hz, 1 H), 7.25 (s, 1 H), 7.23 (d, *J* = 9.6 Hz, 1 H), 6.70 (d, *J* = 9.6 Hz, 1 H), 5.60-6.10 (m, 3H), 4.69 (d, *J* = 7.2 Hz, 1 H), 4.39 (dd, *J* = 12.0, 6.0 Hz, 1 H), 4.2 (d, J = 9.6 Hz, 1 H), 4.03-4.10 (m, 1 H), 3.94 (s, 3H), 3.12-3.28 (m, 1 H), 2.89-3.05 (m, 1 H), 2.50-2.76 (m, 2H), 2.30-0.80 (m, 19H), 1.36 (s, 3H) 1.25 (t, *J* = 7.2 Hz, 3H), 1.10 (s, 3H), 1.04 (s, 9H).

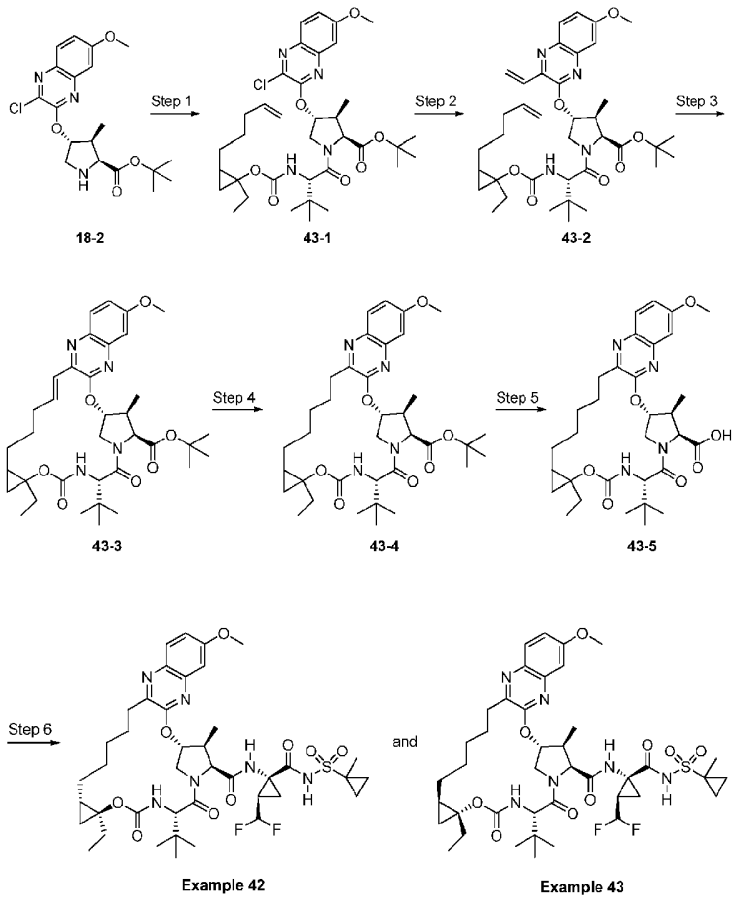
[0239] Example **41.** Preparation of (3aR,7S,10S,11S,12R,24aR)-7-tert-butyl-N-[(1R,2S)-2-(2,2-difluoroethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-11-ethyl-16-methoxy-3a methyl-5,8-dioxo-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10H-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide.



Example 41

[0240] Example **41** was prepared in a similar fashion to Example **39,** substituting Intermediate **A8** for Intermediate **A10** in Step 8. Example **41** was isolated (4.3 mg) in approximately 92% purity. Analytic HPLC RetTime: 9.36 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{42}H_{59}F_2N_6O_9S$: 889.4; found: 889.5. ^{1}H NMR (300 MHz, CD_3COCD_3) δ 7.83 (d, *J* = 7.83 Hz, 1 H), 7.19-7.30 (m, 1 H), 5.74-6.30 (m, 3H), 4.70 (d, *J* = 7.2 Hz, 1 H), 4.19 (dd, *J* = 12.0, 6.0 Hz, 1 H), 4.24 (d, *J* = 9.6 Hz, 1 H), 4.12 *(d, J* = 12.0, 9.6 Hz, 1 H), 3.96 (s, 3H), 3.10-3.26 (m, 1 H), 2.56-2.80 (m, 2H), 2.30-0.80 (m, 25H), 1.54 (s, 3H), 1.42 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H), 1.06 (s, 9H).

[0241] Example **42** and Example **43.** Preparation of (1aS,5S,8S,9S,10R,22aS)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-1a-ethyl-14-methoxy-9-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide and (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-1a-ethyl-14-methoxy-9-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide



Step 1. Preparation of **43-1:** To a solution of Intermediate mixture **D15** (281 mg, 0.81 mmol) and Intermediate **18-2** (290 mg, 0.74 mmol) in MeCN (3.7 mL) was added HATU (308 mg, 0.81 mmol) followed by DIPEA (640 µL, 3.68 mmol) at rt under an argon atmosphere. After 17 h, the reaction mixture was concentrated *in vacuo,* and the crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes) to afford **43-1** (121 mg, 1:1 diastereomeric mixture) as a colorless oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{36}H_{52}ClN_4O_7$: 687.3; found: 687.5.

Step 2. Preparation of **43-2:** To a solution of diastereomeric mixture **43-1** (121 mg, 176 µmol), TEA (38 µL, 264 µmol) and potassium vinyltrifluoroborate (35.4 mg, 264 µmol) in EtOH (0.88 mL) was added $PdCl_2$(dppf) (14.4 mg, 17.6 µmol). The reaction mixture was degassed with argon for 10 min and heated to 78 °C. After 25 min, the reaction mixture was allowed to cool to rt and was concentrated *in vacuo.* The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes) to afford **43-2** (105 mg, 1:1 diastereomeric mixture) as a yellow oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{38}H_{55}N_4O_7$: 679.4; found: 679.5.

Step 3. Preparation of **43-3:** To a solution of diastereomeric mixture **43-2** (105 mg, 155 µmol) in DCE (31 mL) was added Zhan 1B catalyst (11.3 mg, 15.5 µmol, Strem) and the reaction mixture was degassed for 10 minutes with argon. The reaction mixture was then heated to 100 °C. After 15 min, the reaction mixture was allowed to cool to rt and was concentrated *in vacuo.* The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes) to afford **43-3** (52.3 mg, 1:1 diastereomeric mixture) as a light yellow oil. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{51}N_4O_7$: 651.4; found: 651.5.

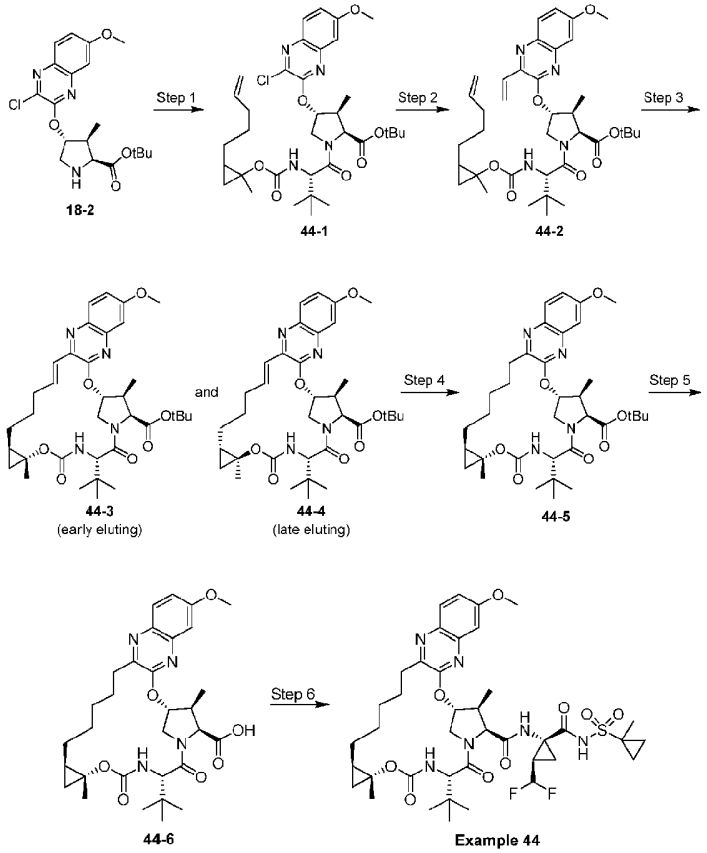
Step 4. Preparation of **43-4:** To a solution of diastereomeric mixture **43-3** (52 mg, 80 µmol) in ethanol (0.4 mL) was added Pd/C (10 wt % Pd, 9 mg, 8 µmol) at rt under an argon atmosphere. The atmosphere was replaced with hydrogen and the reaction mixture was stirred vigorously at rt. After 45 min, the reaction mixture was diluted with ethyl acetate (1 mL) and was filtered through a pad of Celite with ethyl acetate washings (3 × 1 mL). The filtrate was concentrated *in vacuo* to afford **43-4** (49 mg, 1:1 diastereomeric mixture), which was used directly in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{52}N_4O_7$: 653.4; found: 653.6.

Step 5. Preparation of **43-5:** To a solution of diastereomeric mixture **43-4** (49 mg, 67 µmol) in DCM (0.5 mL) was added TMSOTf (60 µL, 0.34 mmol) at rt under an argon atmosphere. After 3 h, the reaction mixture was added slowly to a 0.25 N aqueous NaOH solution (precooled to 0 °C, 1 mL). The resulting mixture was diluted with 1 N aqueous HCl solution (5 mL), and was extracted with

DCM (3 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated to afford **43-5** (71 mg, 1:1 diastereomeric mixture) as a tan solid, which was used directly in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{45}N_4O_7$: 597.3; found: 597.5.

Step 6. Preparation of Examples **42** and **43:** To a solution of diastereomeric mixture **43-5** (71 mg, ~67 µmol) and Intermediate **A10** (54 mg, 178 µmol) in MeCN (1.00 mL) was added HATU (69 mg, 178 µmol) followed by DIPEA (155 µL, 0.89 mmol) at rt under an argon atmosphere. After 1 h, the reaction mixture was concentrated *in vacuo,* and the crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes). The fractions containing the desired product were combined and repurified by preparatory HPLC (Gemini 5u C18 110Å column, 50-100% MeCN/H_2O, 0.1% trifluoroacetic acid modifier) and were lyophilized to afford Example **42** (10 mg) and Example **43** (10 mg) as off white powders. Example **42:** Analytic HPLC RetTime: 9.04 min. $[M+H]^+$ calcd for $C_{41}H_{57}F_2N_6O_9S$: 847.4; found: 847.6. ^1H NMR (400 MHz, CD_3OD) δ 8.98 (s, 1 H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.20 - 7.13 (m, 2H), 5.70 (td, *J* = 55.8, 6.4 Hz, 1 H), 5.65 (d, *J* = 3.7 Hz, 1 H), 5.44 (br s, 1 H), 4.55 - 4.42 (m, 1 H), 4.20 - 4.03 (m, 1 H), 3.87 (s, 3H), 3.17 - 3.08 (m, 1 H), 2.85 - 2.72 (m, 1 H), 2.71 - 2.59 (m, 1 H), 2.18 - 2.06 (m, 1 H), 2.03 - 1.83 (m, 4H), 1.80 - 1.53 (m, 5H), 1.50 (br s, 3H), 1.46 (s, 3H), 1.40 - 1.31 (m, 1 H), 1.33 - 1.09 (m, 5H), 1.06 (s, 9H), 1.05 - 0.95 (m, 6H), 0.92 - 0.73 (m, 3H). Example **43:** Analytic HPLC RetTime: 9.17 min. $[M+H]^+$ calcd for $C_{41}H_{57}F_2N_6O_9S$: 847.4; found: 847.6. ^1H NMR (400 MHz, CD_3OD) δ 9.03 (s, 1 H), 7.68 (d, *J* = 9.5 Hz, 1 H), 7.14 - 7.09 (m, 2H), 5.68 (td, J_{H-F} = 55.5, 6.7 Hz, 1 H), 5.59 (d, *J* = 3.7 Hz, 1 H), 4.45 (d, *J* = 6.8 Hz, 1 H), 4.29 *(d, J* = 12.1 Hz, 1H), 4.12 (s, 1 H), 4.08 (dd, *J* = 12.1, 4.3 Hz, 1 H), 3.82 (s, 3H), 2.90 - 2.79 (m, 1 H), 2.79 - 2.70 (m, 1 H), 2.66 - 2.56 (m, 1 H), 2.43 - 2.31 (m, 1 H), 1.95 - 1.85 (m, 2H), 1.75 - 1.62 (m, 1 H), 1.61 - 1.42 (m, 5H), 1.44 (br s, 3H) 1.40 (s, 3H), 1.34 - 1.02 (m, 8H), 1.00 (s, 9H), 0.99 - 0.89 (m, 5H), 0.85 - 0.74 (m, 3H).

[0242] Example **44.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-14-methoxy-1a,9-dimethyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Step 1. Preparation of **44-1:** HATU (544 mg, 1.43 mmol, Oakwood) and DIPEA (0.83 mL, 4.76 mmol) were added to a mixture of **18-2** (429 mg, 1.09 mmol) and an Intermediate mixture **D6** (395 mg, 1.33 mmol) in 12 mL of acetonitrile under argon. After stirring overnight, the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel

chromatography (0-30% ethyl acetate in hexanes) to produce **44-1** (545 mg; 1:1 mixture of diastereomers) as a white solid. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{35}H_{50}ClN_4O_7$: 673.33; found: 673.47.

Step 2. Preparation of **44-2:** $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (74 mg, 0.091 mmol, Strem) was added to a deoxygenated mixture of **44-1** (542 mg, 0.805 mmol), potassium vinyltrifluoroborate (168 mg, 1.25 mmol), and triethylamine (0.170 mL, 1.21 mmol) in 9 mL of EtOH at room temperature. Reaction mixture was heated at 78 °C under argon for 75 minutes. After cooling to rt, 6 mL of toluene was added and reaction mixture was concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-35% ethyl acetate in hexanes) to yield **44-2** (438 mg; 1:1 mixture of diastereomers) as a yellow film. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{37}H_{53}N_4O_7$: 665.38; found: 665.55.

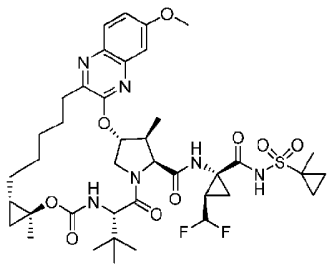
Step 3. Preparation of **44-3** and **44-4:** A diastereomeric mixture **44-2** (437 mg, 0.658 mmol) and Zhan 1B catalyst (81 mg, 0.072 mmol, Strem) in 131 mL of DCE was deoxygenated under argon for 25 minutes. The mixture was then heated at 95 °C for 50 minutes. An additional 7 mg of Zhan 1B catalyst was added and reaction mixture was heated at 95 °C for 10 minutes. After cooling to room temperature, reaction mixture was concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-40% ethyl acetate in hexanes) to yield single diastereomers **44-3** (143 mg, early eluting component) as a light yellow film and **44-4** (118 mg, late eluting component) as a light yellow solid. Early eluting **44-3:** LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{35}H_{49}N_4O_7$: 637.35; found: 637.45. Late eluting **44-4:** LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{35}H_{49}N_4O_7$: 637.35; found: 637.59.

Step 4. Preparation of **44-5:** Palladium on carbon (10 wt % Pd, 48 mg, 0.045 mmol) was added to a solution of **44-3** (143 mg, 0.225 mmol) in 6 mL of ethanol. The atmosphere was replaced with hydrogen and the reaction stirred for 90 minutes. The reaction mixture was filtered over Celite and washed with ethyl acetate. Filtrate was concentrated *in vacuo* to yield **44-5** (130 mg) as brown solid film, which was used in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{35}H_{51}N_4O_7$: 639.37; found: 639.53.

Step 5. Preparation of **44-6:** TMSOTf (0.53 mL, 2.91 mmol) was added dropwise to a solution of **44-5** (130 mg, 1.27 mmol) in 3.8 mL of dichloromethane under argon at room temperature. After one hour, an additional 0.22 mL of TMSOTf was added. After an additional hour, 0.20 mL of TMSOTf was added. After 40 minutes, 0.25 mL of TMSOTf was added. After one hour, reaction mixture was taken up in 10 mL of dichloromethane and quenched by addition of 20 mL of 1 N aqueous HCl with stirring. Layers were separated and aqueous was extracted with dichloromethane (3 x 30 mL). Combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield **44-6** (113 mg) as an off white solid, which was used in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{43}N_4O_7$: 583.31; found: 583.45.

Step 6. Preparation of Example **44:** HATU (53 mg, 0.139 mmol) and DIPEA (0.080 mL, 0.459 mmol) were added to a mixture of **44-6** (51 mg, 0.088 mmol) and Intermediate **A10** (49 mg, 0.161 mmol) in 1.5 mL of MeCN under argon. After stirring for overnight, an additional 13 mg of Intermediate **A10** was added. After one hour, reaction mixture was taken up in 15 mL of ethyl acetate and poured into 20 mL of 1 N aqueous HCl. Layers were separated and aqueous was extracted three times with ethyl acetate. Combined organics were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-40% ethyl acetate in hexanes) to yield Example **44** (41 mg) as an off white solid. Analytic HPLC RetTime: 8.86 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{40}H_{55}F_2N_6O_9S$: 833.36; found: 833.51. ^{1}H NMR (400 MHz, CD_3OD): 7.79 (d, J = 10 Hz, 1 H), 7.28-7.21 (m, 2H), 6.77 (d, J = 8.4 Hz, 1 H), 5.81 (td, J_{H-F} = 56 Hz, J = 6.4 Hz, 1 H), 5.73-5.70 (m, 1 H), 4.56 (d, J = 7.2 Hz, 1 H), 4.40 (d, J = 11.6 Hz, 1 H), 4.26-4.16 (m, 2H), 3.93 (s, 3H), 3.05-2.91 (m, 1 H), 2.90-2.82 (m, 1 H), 2.77-2.68 (m, 1 H), 2.06-1.94 (m, 2H), 1.88-1.74 (m, 1 H), 1.72-1.58 (m, 3H), 1.58-1.44 (m, 4H), 1.53 (s, 3H), 1.51 (s, 3H), 1.43-1.36 (m, 1 H), 1.12-1.02 (m, 2H), 1.09 (s, 9H), 1.07 (d, J = 4 Hz, 3H), 1.00-0.94 (m, 2H), 0.92-0.84 (m, 3H), 0.16-0.11 (m, 1 H).

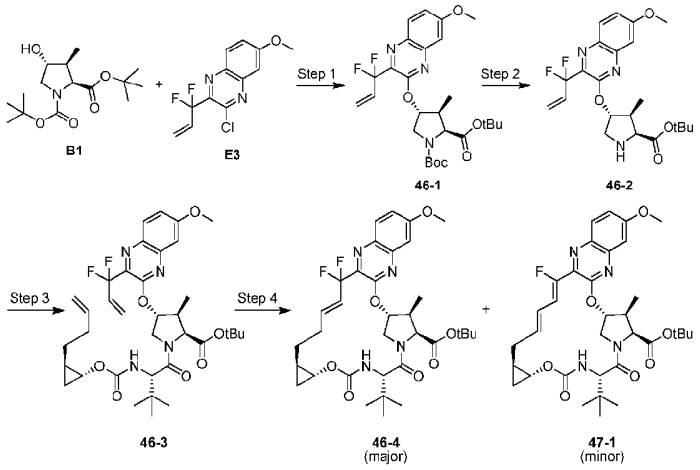
[0243] Example **45.** Preparation of (1aS,5S,8S,9S,10R,22aS)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-14-methoxy-1a,9-dimethyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.

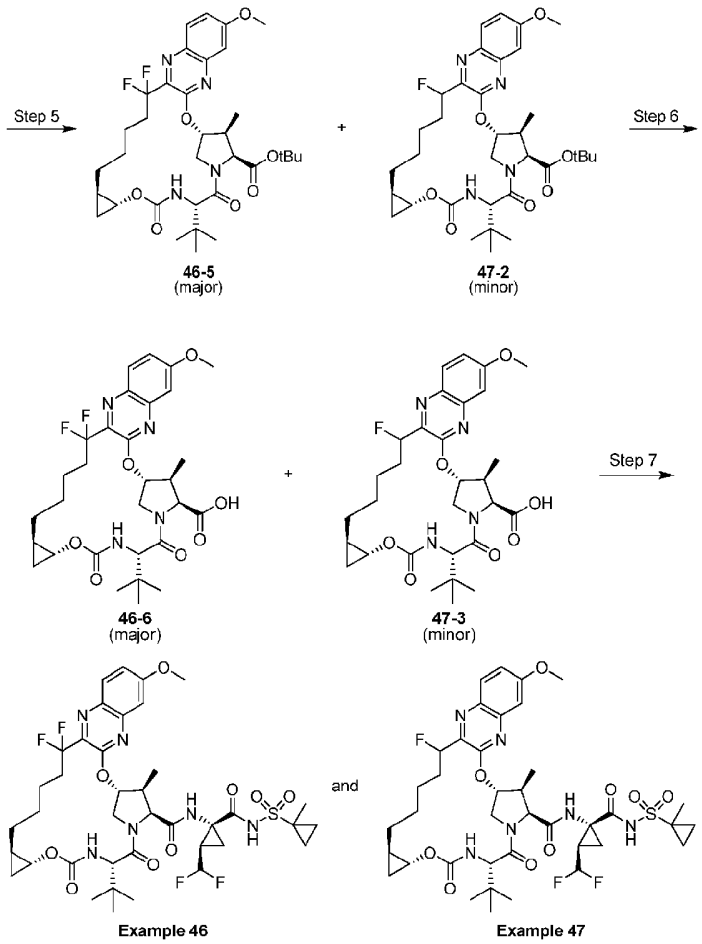


Example 45

[0244] Example **45** was prepared in a similar fashion to Example **44,** substituting late eluting **44-4** for early eluting **44-3** in step 4. Example **45** was isolated (23 mg) as an off white solid. Analytic HPLC RetTime: 8.92 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{40}H_{55}F_2N_6O_9S$: 833.36; found: 833.54. ^{1}H NMR (400 MHz, CD_3OD): 7.79 (d, J = 9.2 Hz, 1 H), 7.25-7.19 (m, 2H), 6.55 (d, J = 5.2 Hz, 1 H), 5.78 (td, J_{H-F} = 61 Hz, J = 6Hz, 1 H), 5.52-5.48 (m, 1 H), 4.58 (d, J = 6.4 Hz, 1 H), 4.52 (d, J = 12 Hz, 1 H), 4.17-4.10 (m, 1 H), 4.04 (d, J = 6.4 Hz, 1 H), 3.93 (s, 3H), 3.22-3.14 (m, 1 H), 2.88-2.80 (m, 1 H), 2.78-2.66 (m, 1 H), 2.08-1.90 (m, 2H), 1.76-1.64 (m, 1 H), 1.63-1.50 (m, 7H), 1.51 (s, 3H), 1.47-1.36 (m, 2H), 1.46 (s, 3H), 1.18-1.06 (m, 1 H), 1.12 (s, 9H), 1.07 (m, 3H), 1.00-0.80 (m, 4H), 0.10-0.04 (m, 1 H).

[0245] Example **46** and **47.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-18,18-difluoro-14-methoxy-9-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide and (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-18-fluoro-14-methoxy-9-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.





Step 1. Preparation of **46-1:** A mixture of Intermediate **B1** (627 mg, 2.08 mmol), Intermediate **E3** (548 mg, 1.91 mmol) and cesium carbonate (744 mg, 2.28 mmol) in 7 mL of DMF was stirred at 85 °C under argon for 36 hours. Reaction mixture was cooled to room temperature and poured into 30 mL of water and aqueous was extracted with ethyl acetate (3 x 30 mL). Combined organics were washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-30% ethyl acetate in hexanes) to yield **46-1** (891 mg) as a white solid. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{27}H_{36}F_2N_3O_6$: 536.25; found: 536.35.

Step 2. Preparation of **46-2:** Quinoxaline ether **46-1** (478 mg, 0.893 mmol) was dissolved in 4.2 mL of tert-butyl acetate and 1.1 mL of dichloromethane at room temperature. $MeSO_3H$ (0.30 mL, 4.67 mmol) was added dropwise and reaction mixture stirred at rt for 2 h. The reaction mixture was transferred to a stirred mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ (30 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford amine **46-2** as a yellow solid film (346 mg). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{22}H_{28}F_2N_3O_4$: 436.20; found: 436.29.

Step 3. Preparation of **46-3:** HATU (396 mg, 1.04 mmol, Oakwood) and DIPEA (0.57 mL, 3.29 mmol) were added to a mixture of **46-2** (345 mg, 0.793 mmol) and Intermediate **D11** (260 mg, 0.965 mmol) in 9 mL of acetonitrile under argon. After stirring overnight, the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (0-40% ethyl acetate in hexanes) to yield **46-3** (545 mg) as a clear solid film. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{49}F_2N_4O_7$: 687.35; found: 687.57.

Step 4. Preparation of **46-4:** A mixture of **46-3** (480 mg, 0.699 mmol) and Zhan 1B catalyst (61 mg, 0.083 mmol, Strem) in 140 mL of DCE was deoxygenated with argon for 18 minutes. The mixture was then heated at 95 °C for 70 minutes. An additional 20 mg of Zhan 1B catalyst was added and mixture stirred at 95 °C for one hour. After cooling to room temperature, reaction mixture was concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-35% ethyl acetate in hexanes) to yield an inseparable mixture of **46-4** (major), and approximately 15% of **47-1** (minor; 233 mg total) as an off white solid. Major

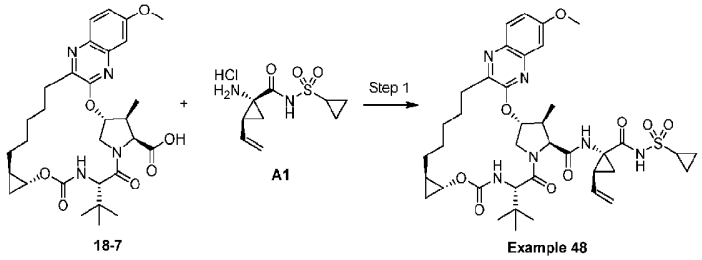
component **46-4:** LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{34}H_{45}F_2N_4O_7$: 665.38; found: 665.50. Minor component **47-1:** LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{34}H_{44}FN_4O_7$: 639.31; found: 639.49.

Step 5. Preparation of mixture of **46-5** and **47-2:** Palladium on carbon (10 wt % Pd, 70 mg, 0.066 mmol) was added to a solution of the mixture of **46-4** and **47-1** (232 mg, 0.353 mmol) from the previous step in 9 mL of ethanol. The atmosphere was replaced with hydrogen and stirred for 7 h. The reaction was filtered over Celite, washing with ethanol. Filtrate was concentrated *in vacuo* to yield a mixture of **46-5** (major) and **47-2** (minor; 216 mg total) as an off white solid, which was used in the next step without further purification. Major component **46-5:** LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{34}H_{47}F_2N_4O_7$: 661.33; found: 661.52. Minor component **47-2:** LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{34}H_{48}FN_4O_7$: 643.34; found: 643.57.

Step 6. Preparation of mixture of **46-6** and **47-3:** TMSOTf (0.35 mL, 1.90 mmol) was added dropwise to a solution of a mixture of **46-5** and **47-2** (215 mg, 0.326 mmol) from the previous step in 6.5 mL of dichloromethane under argon at rt. After 1 h, an additional 0.18 mL of TMSOTf was added. After an additional hour, 0.30 mL of TMSOTf was added. After 2 h, 0.18 mL of TMSOTf was added. After 1 h, an additional 0.18 mL of TMSOTf was added. After 45 minutes, reaction mixture was taken up in 25 mL of dichloromethane and quenched by addition of 30 mL of 1 N aqueous HCl with stirring. The aqueous layer was extracted with dichloromethane (3 x 40 mL). Combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield an inseparable mixture of **46-6** (major) and **47-3** (minor; 187 mg total), which was used in the next step without further purification. Major component **46-6:** LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{30}H_{39}F_2N_4O_7$: 605.27; found: 605.44. Minor component **47-3:** LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{30}H_{39}FN_4O_7$: 587.28; found: 587.38.

Step 7. Preparation of Example **46** and Example **47:** HATU (160 mg, 0.421 mmol, Oakwood) and DIPEA (0.25 mL, 1.44 mmol) were added to a mixture of **46-6** and **47-3** (150 mg, 0.248 mmol) from the previous step and Intermediate **A10** (150 mg, 0.496 mmol) in 6.5 mL of acetonitrile under argon. After stirring for overnight, reaction mixture was taken up in 30 mL of ethyl acetate and poured into 30 mL of 1 N aqueous HCl. The aqueous layer was extracted three times with ethyl acetate. Combined organics were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-50% ethyl acetate in hexanes) and reverse phase prep HPLC (50-100% acetonitrile in water, with 0.1% trifluoroacetic acid buffer) to yield the trifluoroacetic acid salt of Example **46** (107 mg) as a light yellow solid and the trifluoroacetic acid salt of the 1:1 mixture of diastereomers of Example **47** (12 mg) as a light yellow solid. Example **46:** Analytic HPLC RetTime: 8.60 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{39}H_{51}F_4N_6O_9S$: 855.33; found: 855.63. ^{1}H NMR (400 MHz, CD_3OD): δ 9.23 (s, 1 H), 7.94 (d, J = 9.2 Hz, 1 H), 7.31 (dd, J = 9.2, 2.8 Hz, 1 H), 7.28 (d, J = 2.8 Hz, 1 H), 5.78 (td, J_{H-F} = 66 Hz, J = 6.8 Hz, 1 H), 5.68-5.66 (m, 1 H), 4.57 (d, J = 6.4 Hz, 1 H), 4.41 (d, J = 12 Hz, 1 H), 4.35 (s, 1 H), 4.22-4.16 (dd, J = 12, 4 Hz, 1 H), 3.97 (s, 3H), 3.72-3.66 (m, 1 H), 2.86-2.76 (m, 1 H), 2.64-2.48 (m, 1 H), 2.11-1.94 (m, 3H), 1.86-1.74 (m, 3H), 1.73-1.62 (m, 1 H), 1.58-1.54 (m, 2H), 1.50 (s, 3H), 1.49-1.44 (m, 1 H), 1.42-1.38 (m, 1 H), 1.11-1.04 (m, 4H), 1.09 (s, 9H), 1.02-0.94 (m, 2H), 0.93-0.86 (m, 2H), 0.78-0.66 (m, 1 H), 0.54-0.46 (m, 1 H). Example **47** (1:1 mixture of diastereomers): Analytic HPLC RetTime: 8.45 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{39}H_{52}F_3N_6O_9S$: 837.34; found: 837.63. ^{1}H NMR (400 MHz, CD_3OD): δ 9.13 (s, 1 H), 7.89 (d, J = 8.8 Hz, 1 H), 7.27 (dd, J = 9.2, 2.8 Hz, 1 H), 7.24 (d, J = 2.8 Hz, 1 H), 5.99-5.43 (m, 1 H), 5.79 (td, J_{H-F} = 55 Hz, J = 6.8 Hz, 1 H), 5.53-5.50 (m, 1 H), 4.57-4.44 (m, 2H), 4.11 (s, 1 H), 4.35 (s, 1 H), 4.22-4.13 (dd, J = 12.4, 4 Hz, 1 H), 3.95 (s, 3H), 3.83-3.79 (m, 1 H), 2.94-2.80 (m, 2H), 2.28-2.14 (m, 1 H), 2.06-1.96 (m, 2H), 1.88-1.69 (m, 4H), 1.58-1.54 (m, 2H), 1.51 (s, 3H), 1.44-1.36 (m, 1 H), 1.32-1.26 (m, 1 H), 1.14-1.04 (m, 4H), 1.10 (s, 9H), 1.02-0.86 (m, 4H), 0.74-0.64 (m, 1 H), 0.58-0.48 (m, 1 H).

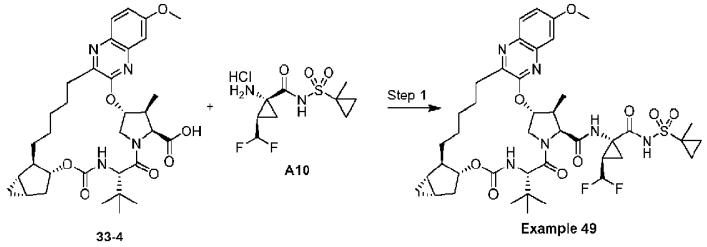
[0246] Example **48.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-{(1R,2S)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-14-methoxy-9-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Step 1: Preparation of Example **48:** To a suspension of acid **18-7** (9.7 mg, 0.017 mmol) and Intermediate **A1** (13 mg, 0.049 mmol) in MeCN (0.4 mL) was added DIPEA (40 µL, 0.23 mmol). To the resulting solution was added HATU (12.5 mg, 0.033 mmol). The

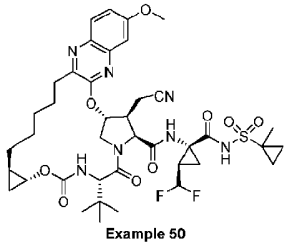
reaction was stirred at rt for 1 h and was diluted with EtOAc (2 mL), 0.2 M aqueous HCl (1 mL), and brine (1 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a crude residue that was dissolved in CH_2Cl_2 and adsorbed onto 1 g silica gel. Purification by silica gel chromatography (10% to 50% acetone in hexanes) provided a residue that was lyophilized from water and MeCN to provide Example **48** as a white amorphous solid (8.4 mg). Analytic HPLC RetTime: 8.52 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{39}H_{53}N_6O_9S$: 781.4; found: 781.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1 H), 7.83 (d, *J* = 9.1 Hz, 1 H), 7.19 (dd, *J* = 9.1, 2.7 Hz, 1 H), 7.10 (d, *J* = 2.7 Hz, 1 H), 6.73 (s, 1 H), 5.86 - 5.72 (m, 1 H), 5.57 (d, *J* = 3.8 Hz, 1 H), 5.48 (d, *J* = 9.9 Hz, 1 H), 5.27 - 5.15 (m, 1 H), 5.15 - 5.07 (m, 1 H), 4.48 - 4.35 (m, 3H), 4.12 (dd, *J* = 11.8, 4.1 Hz, 1 H), 3.94 (s, 3H), 3.81 - 3.71 (m, 1 H), 2.98 - 2.75 (m, 4H), 2.16 - 2.09 (m, 1 H), 1.94 (dd, *J* = 8.2, 5.8 Hz, 1 H), 1.87 - 1.24 (m, 9H), 1.17 (d, *J* = 7.4 Hz, 3H), 1.09 (s, 9H), 1.04 - 0.91 (m, 5H), 0.75 - 0.65 (m, 1 H), 0.52 - 0.42 (m, *J* = 6.0 Hz, 1 H).

[0247] Example **49.** Preparation of (1aS,2aR,6S,9S,10S,11R,23aR,23bS)-6-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-15-methoxy-10-methyl-4,7-dioxo-1a,2,2a,4,5,6,7,10,11,19,20,21,22,23,23a,23b-hexadecahydro-1H,9H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19][1,10,3,6]dioxadiazacyclononade cino[11,12-b]quinoxaline-9-carboxamide.



[0248] Step 1: Preparation of Example **49:** To a suspension of acid **33-4** (30 mg, 0.049 mmol) and Intermediate **A10** (31 mg, 0.10 mmol) in MeCN (700 µL) was added DIPEA (70 µL, 0.40 mmol). HATU (32 mg, 0.084 mmol) was added to the resulting solution, and the reaction was stirred at rt for 1.5 h. An additional portion of Intermediate **A10** (6 mg, 0.02 mmol) was then added. The reaction was stirred an additional 30 min and was then diluted with EtOAc (30 mL), 0.2 M aqueous HCl (15 mL) and brine (15 mL). The phases were separated and the aqueous phase was extracted with EtOAc (30 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a crude residue. This residue was dissolved in CH_2Cl_2 and adsorbed onto 2 g silica gel. Purification by silica gel chromatography (10% to 50% acetone in hexanes) provided an amorphous residue that was lyophilized from water and MeCN to provide Example **49** as a white amorphous solid (30.5 mg). Analytic HPLC RetTime: 9.15 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{42}H_{57}F_2N_6O_9S$: 859.4; found: 859.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1 H), 7.82 (d, *J* = 9.1 Hz, 1 H), 7.45 (s, 1 H), 7.18 (dd, *J* = 9.1, 2.7 Hz, 1 H), 7.08 (d, *J* = 2.7 Hz, 1 H), 6.14 - 5.71 (m, 1 H), 5.61 (d, *J* = 3.7 Hz, 1 H), 5.28 (d, *J* = 9.8 Hz, 1 H), 5.00 (d, *J* = 7.4 Hz, 1 H), 4.49 (d, *J* = 7.0 Hz, 1 H), 4.42 - 4.31 (m, 2H), 4.12 (dd, *J* = 11.6, 4.0 Hz, 1 H), 3.93 (s, 3H), 3.00 - 2.63 (m, 4H), 2.25 - 2.16 (m, 1 H), 2.09 - 1.90 (m, 4H), 1.81 - 0.95 (m, 26H), 0.92 - 0.75 (m, 3H), 0.57 - 0.45 (m, 1 H), 0.44 - 0.36 (m, 1 H).

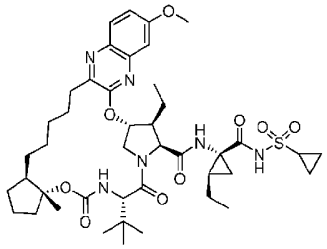
[0249] Example **50.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-9-(cyanomethyl)-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



[0250] Example **50** was prepared in a similar fashion to Example **1,** substituting Intermediate **B8** for Intermediate **B4** in step 1. Example **50** was purified by reverse phase HPLC (Gemini column, 58-98 % ACN/H_2O + 0.1% TFA) and lyophilized to afford solid

(5 mg) as a TFA salt. Analytic HPLC RetTime: 8.29 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{40}H_{51}F_2N_7O_9S$: 844.94; found: 844.58. ^1H NMR (400 MHz, CD_3OD) δ 9.71 (s, 1 H), 7.79 (d, *J* = 8.8 Hz, 1 H), 7.22 (m, 2H), 6.25 (m, 1 H), 6.08 - 5.80 (m, 1 H), 4.39 (m, 1 H), 4.29 (m, 2H), 4.13 (m, 1 H), 3.92 (s, 3H), 3.65 (m, 1 H), 3.06 - 2.83 (m, 4H), 2.55 (m, 1 H), 2.14 - 1.47 (m, 17H), 1.03(s, 9H), 0.92 (m, 4H), 0.65 (m, 1 H), 0.45 - 0.43 (m, 1 H).

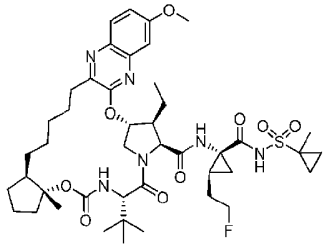
[0251] Example **51.** Preparation of (3aR,7S,10S,11S,12R,24aR)-7-tert-butyl-N-{(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethylcyclopropyl}-11-ethyl-16-methoxy-3a-methyl-5,8-dioxo-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10H-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide.



Example 51

[0252] Example **51** was prepared in a similar fashion to Example **39,** substituting Intermediate **A3** for Intermediate **A10** in step 8. Example **51** was isolated (12.3 mg) in approximately 96.5% purity. Analytic HPLC RetTime: 9.38 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{43}H_{63}N_6O_9S$: 839.4; found: 839.5. ^1H NMR (300 MHz, CD_3OD) δ 7.60 (d, *J* = 8.4 Hz, 1 H), 6.98-7.08 (m, 2H), 6.53 (d, *J* = 9.6 Hz, 1 H), 5.57-5.83 (m, 2H), 4.52 (d, *J* = 8.4 Hz, 2H), 4.24 (dd, *J* = 10.8, 6.0 Hz, 1 H), 4.02 (d, *J* = 9.6 Hz, 1 H), 3.82 (dd, *J* = 10.8, 2.4 Hz, 1 H), 3.73 (s, 3H), 2.93-3.10 (m, 1 H), 2.80-2.90 (m, 2H), 2.30-2.58 (m, 2H), 0.60-2.10 (m, 32H), 0.84 (s, 9H).

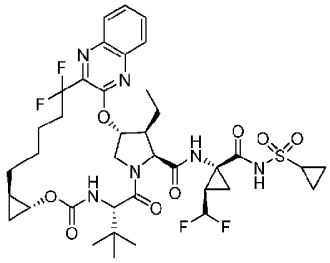
[0253] Example **52.** Preparation of (3aR,7S,10S,11S,12R,24aR)-7-tert-butyl-11-ethyl-N-[(1R,2S)-2-(2-fluoroethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-16-methoxy-3a-methyl-5,8-dioxo-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10H-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide.



Example 52

[0254] Example **52** was prepared in a similar fashion to Example **39,** substituting Intermediate **A6** for Intermediate **A10** in step 8. Example **52** was isolated (12.3 mg) in approximately 96.5% purity. Analytic HPLC RetTime: 8.60 min. Analytic HPLC RetTime: 9.31 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{44}H_{64}FN_6O_9S$: 871.4; found: 871.5. ^1H NMR (300 MHz, CD_3OD) δ 7.81 (d, *J* = 8.4 Hz, 1 H), 7.20-7.30 (m, 2H), 6.73 (d, *J* = 9.6 Hz, 1 H), 5.75-6.02 (m, 2H), 4.74 (d, *J* = 8.4 Hz, 2H), 4.54 (t, *J* = 6.0 Hz, 2H), 4.36-4.49 (m, 1 H), 4.23 (d, *J* = 9.6 Hz, 1 H), 4.04 (dd, *J* = 12.0, 2.4 Hz, 1 H), 3.75 (s, 3H), 3.28-3.16 (m, 1 H), 2.50-2.70 (m, 2H), 2.30-0.80 (m, 35H), 1.04 (s, 9H).

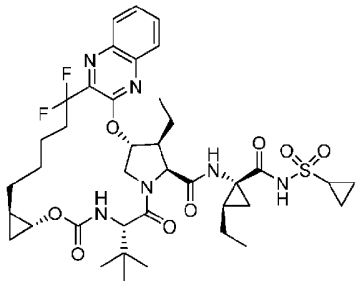
[0255] Example **53.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1 R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-9-ethyl-18,18-difluoro-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 53

[0256] Example **53** was prepared similarly to Example **17** substituting Intermediate **E4** for Intermediate **E3** in Step 1 and Intermediate **A9** for Intermediate **A10** in Step 7. Example **53** was isolated (8.8 mg) as a white solid. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{38}H_{48}F_4N_6O_8S$: 825.32; found: 825.75. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1 H), 8.15 *(d, J* = 8.2 Hz, 1 H), 7.91 - 7.74 (m, 2H), 7.69 (t, *J* = 7.6 Hz, 1 H), 6.92 (s, 1 H), 5.47 (d, *J* = 9.6 Hz, 1 H), 4.48 (t, *J* = 10.3 Hz, 2H), 4.36 (d, *J* = 9.4 Hz, 1 H), 4.12 (dd, *J* = 12.1, 3.6 Hz, 1 H), 3.70 - 3.59 (m, 1 H), 3.08 - 2.75 (m, 1 H), 2.58 - 2.38 (m, 1 H), 2.14 (t, *J* = 6.8 Hz, 1 H), 1.95 - 1.67 (m, 4H), 1.47 (tt, *J* = 13.9, 7.1 Hz, 4H), 1.35 (s, 2H), 1.20 (t, *J* = 7.3 Hz, 3H), 1.15 - 0.64 (m, 19H), 0.51 (q, *J* = 6.4 Hz, 1 H).

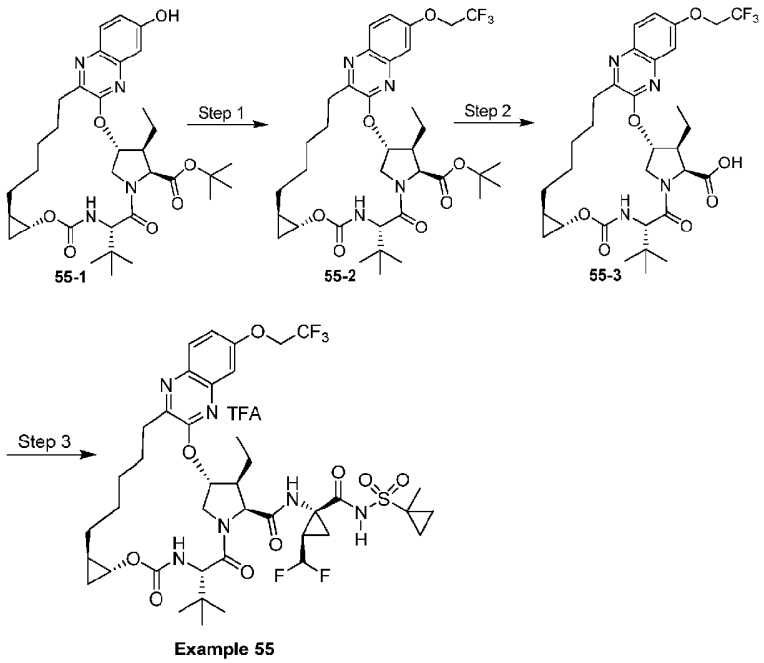
[0257] Example **54.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-{(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethylcyclopropyl}-9-ethyl-18,18-difluoro-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 54

[0258] Example **54** was prepared similarly to Example **53** replacing Intermediate **A9** with Intermediate **A3.** Example **54** was isolated (10.0 mg) as a white solid. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{39}H_{52}F_2N_6O_8S$: 803.35; found: 803.79. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1 H), 8.12 (d, *J* = 8.2 Hz, 1 H), 7.88 - 7.69 (m, 2H), 7.66 (t, *J* = 7.6 Hz, 1 H), 6.68 (s, 1 H), 5.95 (d, *J* = 3.4 Hz, 1 H), 5.46 (d, *J* = 9.4 Hz, 1 H), 4.45 (dd, *J* = 13.8, 9.7 Hz, 2H), 4.09 (dd, *J* = 12.0, 3.6 Hz, 2H), 3.71 - 3.57 (m, 1 H), 2.53 (dd, *J* = 21.4, 14.6 Hz, 1 H), 1.85 - 1.39 (m, 10H), 1.38 - 0.96 (m, 20H), 1.01 (dd, *J* = 17.2, 9.5 Hz, 3H), 1.04 - 0.78 (m, 6H), 0.70 (s, 1 H), 0.49 (dd, *J* = 12.7, 6.3 Hz, 1 H).

[0259] Example **55.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-3,6-dioxo-14-(2,2,2-trifluoroethoxy)-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



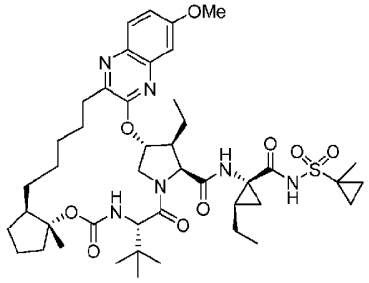
[0260] Intermediate **55-1** was prepared by following Steps 1 through 6 of Example **1,** substituting for Intermediate **E2** for Intermediate **E1** in Step 1. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{49}N_4O_7$: 625.36; found: 625.25.

Step 1. Preparation of **55-2.** Quinoxalinol **55-1** (24 mg, 0.038 mmol) was suspended in DMF (2 mL) and treated with Cs_2CO_3 (63 mg, 0.19 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.055 mL, 0.38 mmol). The reaction mixture was stirred at RT for 5 h, then diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford **55-2,** which was carried on without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{50}F_3N_4O_7$: 707.36; found: 707.38.

Step 2. Preparation of **55-3.** Trifluoroethyl ether **55-2** (0.038 mmol theoretical) was treated with DCM (4 mL) and TMSOTf (0.14 mL, 0.77 mmol) at RT. After 1 h, the reaction was quenched by addition of 1 M NaOH (2 mL). After stirring vigorously for 5 min, the mixture was poured into a separatory funnel followed by 10% HCl (20 mL). The aqueous layer was extracted 3x with DCM. The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford **55-3,** which was carried on without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{32}H_{42}F_3N_4O_7$: 651.30; found: 651.18.

Step 3. Preparation of Example **55.** Carboxcylic acid **55-3** (0.038 mmol theoretical) was treated with intermediate **A10** (23 mg, 0.077 mmol), TBTU (25 mg, 0.077 mmol), DMAP (9 mg, 0.077 mmol), DCM (1 mL) and DIPEA (0.134 mL, 0.768 mmol). The reaction mixture was stirred at RT for 20 h, then concentrated under reduced pressure and purified by reverse phase HPLC to afford Example **55** as a TFA salt (7 mg, 18% over 3 steps). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{41}H_{54}F_5N_6O_9S$: 901.36; found: 902.08. ^{1}H NMR (400 MHz, CD_3OD) δ 9.18 (s, 1 H), 7.86 (d, *J* = 9.1 Hz, 1 H), 7.32 (dd, *J* = 9.1, 2.8 Hz, 1 H), 7.25 (d, *J* = 2.7 Hz, 1 H), 6.02 - 5.63 (m, 2H), 4.76 - 4.62 (m, 2H), 4.56 (d, *J* = 7.1 Hz, 1 H), 4.39 (t, *J* = 6.0 Hz, 2H), 4.15 (dt, *J* = 17.2, 8.6 Hz, 1 H), 3.74 (dd, *J* = 6.7, 2.8 Hz, 1 H), 3.05 - 2.89 (m, 1 H), 2.82 (td, *J* = 13.2, 4.2 Hz, 1 H), 2.65 - 2.50 (m, 1 H), 2.02 (d, *J* = 10.4 Hz, 2H), 1.78 (dt, *J* = 23.5, 10.7 Hz, 3H), 1.68 - 1.26 (m, 14H), 1.22 (t, *J* = 7.3 Hz, 3H), 1.10 (s, 9H), 0.97 (d, *J* = 2.5 Hz, 2H), 0.95 - 0.84 (m, 2H), 0.71 (s, 1 H), 0.51 (t, *J* = 9.8 Hz, 1 H).

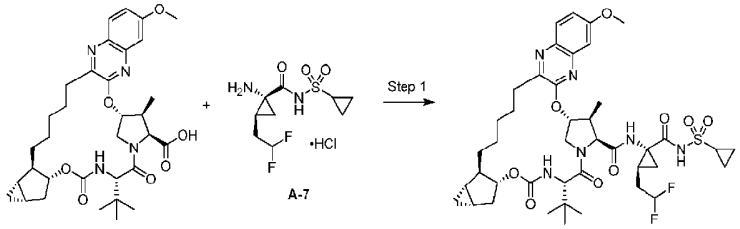
[0261] Example **56.** Preparation of (3aR,7S,10S,11S,12R,24aR)-7-tert-butyl-11-ethyl-N-[(1R,2R)-2-ethyl-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-16-methoxy-3a-methyl-5,8-dioxo-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10H-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide



Example 56

[0262] Example **56** was prepared in a similar fashion to Example **39,** substituting Intermediate **A9** for Intermediate **A3** in Step 8. Example **56** was isolated (8.8 mg, 0.0103 mmol, 53.7%). Analytic HPLC RetTime: 9.56 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{44}H_{65}N_6O_9S$: 853.45; found: 853.5. ^{1}H NMR (300 MHz, CD_3OD) δ 7.81 (d, *J* = 9.6 Hz, 1 H), 7.20-7.30 (m, 2H), 6.73 (d, *J* = 9.6 Hz, 1 H), 5.76-6.01 (m, 2H), 4.75 (d, *J* = 8.4 Hz, 1 H), 4.46 (dd, *J* = 12.0, 6.0 Hz, 1 H), 4.23 (d, *J* = 9.6 Hz, 1 H), 4.00-4.08 (m, 1 H), 3.95 (s, 3H), 2.50-2.78 (m, 3H), 0.80-2.30 (m, 30H), 1.54 (s, 3H), 1.35 (s, 3H), 1.05 (s, 9H).

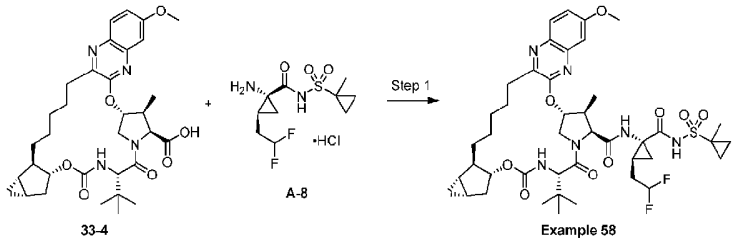
[0263] Example **57.** Preparation of (1aS,2aR,6S,9S,10S,11R,23aR,23bS)-6-tert-butyl-N-[(1R,2S)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(2,2-difluoroethyl)cyclopropyl]-15-methoxy-10-methyl-4,7-dioxo-1a,2,2a,4,5,6,7,10,11,19,20,21,22,23,23a,23b-hexadecahydro-1H,9H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19][1,10,3,6]dioxadiazacyclononade cino[11,12-b]quinoxaline-9-carboxamide.



33-4 A-7 Example 57

[0264] Step 1. Preparation of Example **57.** To a suspension of acid **33-4** (14.9 mg, 0.0245 mmol) and amine hydrochloride **A-7** (16.3 mg, 0.0535 mmol) in MeCN (500 µL) was added DIPEA (40 µL, 0.23 mmol). HATU (15.5 mg, 0.0408 mmol) was added to the resulting solution, and the reaction was stirred at rt for 17 h. The reaction was then diluted with EtOAc (2 mL), 0.2 M aqueous HCl (1.5 mL) and brine (1.5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (4 x 1.5 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue. This residue was dissolved in CH_2Cl_2 and was concentrated onto 1.5 g silica gel. Purification by silica gel chromatography (10% to 40% acetone in hexanes) provided an amorphous residue that was lyophilized from water and MeCN to provide Example **57.** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{42}H_{57}F_2N_6O_9S$: 859.4; found: 859.0. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.82 (d, *J* = 9.1 Hz, 1H), 7.19 (dd, *J* = 9.1, 2.7 Hz, 1 H), 7.09 (d, *J* = 2.6 Hz, 1H), 6.75 (s, 1 H), 6.07 - 5.57 (m, 2H), 5.26 (d, *J* = 9.8 Hz, 1 H), 5.01 (d, *J* = 7.4 Hz, 1H), 4.50 - 4.29 (m, 3H), 4.12 (dd, *J* = 11.7, 3.9 Hz, 1H), 3.93 (s, 3H), 3.00 - 2.62 (m, 4H), 2.34 - 0.96 (m, 33H), 0.95 - 0.78 (m, 1H), 0.51 (dd, *J* = 13.0, 7.9 Hz, 1H), 0.39 (d, *J* = 4.2 Hz, 1 H).

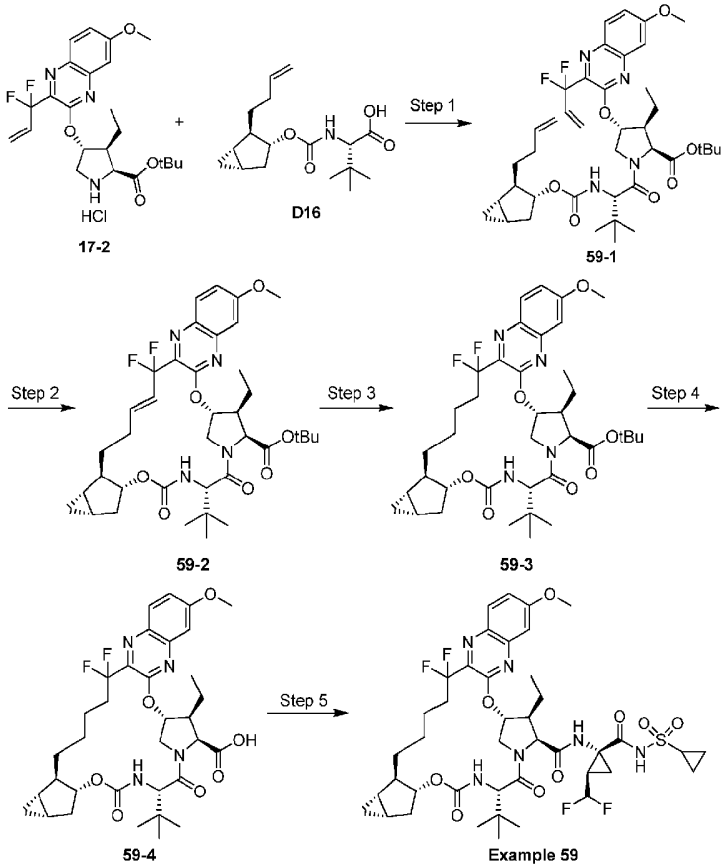
[0265] Example **58.** Preparation of (1aS,2aR,6S,9S,10S,11R,23aR,23bS)-6-tert-butyl-N-[(1R,2S)-2-(2,2-difluoroethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-15-methoxy-10-methyl-4,7-dioxo-1a,2,2a,4,5,6,7,10,11,19,20,21,22,23,23a,23b-hexadecahydro-1H,9H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19][1,10,3,6]dioxadiazacyclononade cino[11,12-b]quinoxaline-9-carboxamide



33-4 A-8 Example 58

[0266] Step 1. Preparation of Example **58.** To a suspension of acid **33-4** (14.5 mg, 0.0238 mmol) and amine hydrochloride **A-8** (16.0 mg, 0.0502 mmol) in MeCN (500 µL) was added DIPEA (40 µL, 0.23 mmol). HATU (15.5 mg, 0.0408 mmol) was added to the resulting solution, and the reaction was stirred at rt for 17 h. The reaction was then diluted with EtOAc (2 mL), 0.2 M aqueous HCl (1.5 mL) and brine (1.5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (4 x 1.5 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue. This residue was dissolved in CH_2Cl_2 and was concentrated onto 1.5 g silica gel. Purification by silica gel chromatography (10% to 40% acetone in hexanes) provided an amorphous residue that was lyophilized from water and MeCN to provide Example **58.** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{43}H_{59}F_2N_6O_9S$: 873.4; found: 873.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.82 (d, *J* = 9.1 Hz, 1 H), 7.19 (dd, *J* = 9.1, 2.7 Hz, 1 H), 7.09 (d, *J* = 2.7 Hz, 1H), 6.82 (s, 1H), 6.12 - 5.54 (m, 2H), 5.25 (d, *J* = 9.8 Hz, 1H), 5.01 (d, *J* = 7.2 Hz, 1H), 4.50 - 4.30 (m, 3H), 4.13 (dd, *J* = 11.7, 4.2 Hz, 1H), 3.93 (s, 3H), 3.03 - 2.65 (m, 4H), 2.34 - 0.97 (m, 33H), 0.94 - 0.76 (m, 3H), 0.60 - 0.45 (m, 1 H), 0.45 - 0.34 (m, 1H).

[0267] Example **59.** Preparation of (1aS,2aR,6S,9S,10S,11R,23aR,23bS)-6-tert-butyl-N-[(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-10-ethyl-19,19-difluoro-15-methoxy-4,7-dioxo-1 a,2,2a,4,5,6,7,10,11,19,20,21,22,23,23a,23b-hexadecahydro-1H,9H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19] [1,10,3,6]dioxadiazacyclononade cino[11,12-b]quinoxaline-9-carboxamide.



Step 1. Preparation of **59-1**. A solution of Intermediate **D16** (0.50 g, 1.6 mmol) in DMF (7 mL) was treated subsequently with COMU (0.80 g, 1.9 mmol), DIPEA (1.2 mL, 6.7 mmol) and Intermediate **17-2** (0.65 g, 1.3 mmol) and stirred overnight at rt. The reaction was quenched with 1 M citric acid solution (5 mL) and extracted with EA. The combined organics were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (15-100% EA/hex) to afford **59-1.** LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{40}H_{55}F_2N_4O_7$: 741.88; found: 741.51.

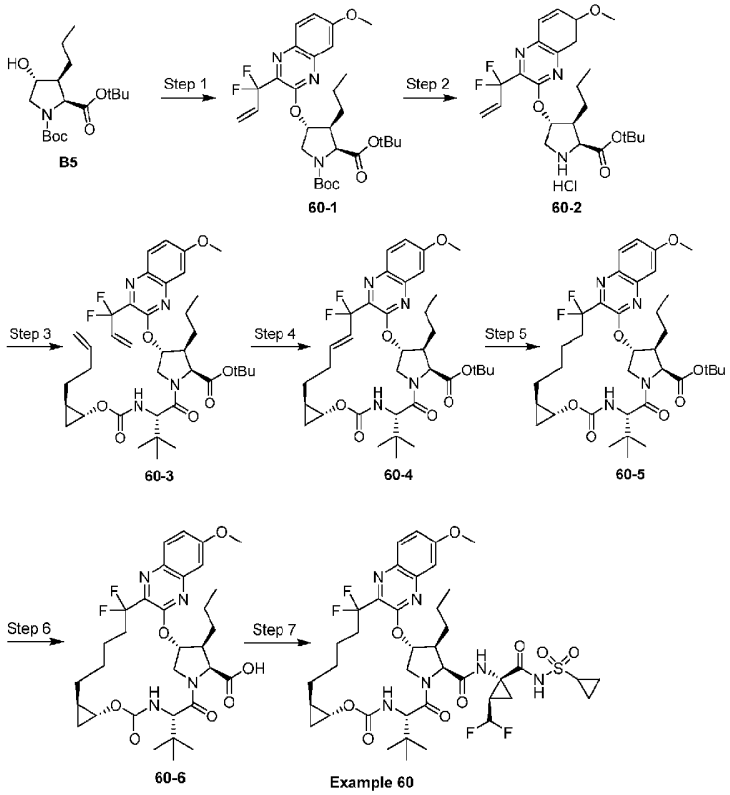
Step 2. Preparation of **59-2.** A solution of **59-1** (0.51 g, 0.69 mmol) in DCE (140 mL) is sparged with argon for 30 min prior to addition of Zhan 1B catalyst (0.051 g, 0.07 mmol). The reaction was heated to 85 °C for 45 min, and another portion of Zhan 1B catalyst was added. After an additional 30 min, the reaction was cooled to rt, concentrated *in vacuo* and purified by silica gel chromatography (5-100% EA/hex) to produce **59-2.** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{38}H_{51}F_2N_4O_7$: 713.83; found: 713.54.

Step 3. Preparation of **59-3.** A solution of **59-2** was taken up in EtOH (8 mL). Pd/C (0.072 g, 10% w/w) was added and the atmosphere replaced with H_2. After 1 h, additional catalyst was added. After 4 h, EA and additional catalyst was added. After an additional 3 h, the reaction was filtered, concentrated *in vacuo,* and the residue taken up in EtOH (8 mL) and treated with 0.5 g Pd/C (10% w/w) and the atmosphere replaced with H_2. The reaction was stirred overnight, and then worked up again as previously described to produce of **59-3** that was used subsequently without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{38}H_{53}F_2N_4O_7$: 715.85; found: 715.52.

Step 4. Preparation of **59-4.** A solution of **59-3** (0.40 g, 0.56 mmol) in DCM (1.5 mL) was treated with 2.5 mL TFA at rt. After 1.5 h, the reaction was concentrated *in vacuo*. The residue was taken up in EA, washed with saturated aqueous $NaHCO_3$, brine and then dried over anhydrous $MgSO_4$. Concentration *in vacuo* produced **59-4** that was used subsequently without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{34}H_{45}F_2N_4O_7$: 659.74; found: 659.56.

Step 5. Preparation of Example **59:** A solution of **59-4** (0.20 g, 0.30 mmol) in DMF (2 mL) was treated subsequently with HATU (0.21 g, 0.55 mmol), DIPEA (0.27 mL, 1.5 mmol), DMAP (0.056 g, 0.46 mmol), and Intermediate **A9** (0.13 g, 0.46 mmol) and stirred for 5 h at rt. The reaction mixture is purified by preparatory HPLC to produce the TFA salt of Example **59**. Analytic HPLC RetTime: 9.20 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{42}H_{55}F_4N_6O_9S$: 895.98; found: 895.60. ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (s, 1 H); 7.94 (d, J = 9.2 Hz, 1 H); 7.32 (dd, J = 9.2, 2.4 Hz, 1 H); 7.21 (d, J = 2.4 Hz, 1 H); 5.98 (br s, 1 H); 5.85 (td, J_{H-F} = 55.2 Hz, J = 6 Hz, 1 H); 4.94 (d, J = 7.6 Hz, 1 H); 4.58 (d, J = 7.2 Hz, 1 H); 4.35 (d, J = 7.2 Hz, 1 H); 4.33 (br s, 1 H); 4.18 (dd, J = 12, 3.6 Hz, 1 H); 3.97 (br s, 3H); 2.98 (m, 1 H); 2.64-2.41 (m, 2H); 2.22 (m, 1 H); 2.15-1.92 (m, 4H); 1.84-1.22 (m, 14H); 1.18 (t, J = 7.2 Hz, 3H); 1.14-0.98 (m, 2H); 1.08 (s, 9H); 0.60-0.48 (m, 2H).

[0268] Example **60.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-18,18-difluoro-14-methoxy-3,6-dioxo-9-propyl-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Step 1. Preparation of **60-1:** To a solution of Intermediate **B5** (160 mg, 0.590 mmol) and Intermediate **E3** (194 mg, 0.590 mmol) in MeCN (2.95 mL) was added cesium carbonate (192 mg, 0.590 mmol) at rt under an argon atmosphere. After 24 h, the reaction mixture was then filtered through a pad of Celite and the filtrate concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford substituted quinoxaline **60-1.** LCMS-ESI$^+$ (m/z):

$[M+H]^+$calcd for $C_{29}H_{40}F_2N_3O_6$: 564.28; found: 564.44.

Step 2. Preparation of **60-2:** To a solution **60-1** (193 mg, 0.343 mmol) in *tert*-butyl acetate (1.36 mL) was added a solution of methanesulfonic acid (111 µL, 1.72 mmol) in dichloromethane (0.34 mL) and the reaction was stirred at rt. After 2 h, the reaction mixture was diluted with saturated sodium bicarbonate solution (20 mL) and the resulting mixture was extracted with ethyl acetate (2 x 20 mL). The combine organics were dried over anhydrous sodium sulfate and were concentrated *in vacuo* to afford amine hydrochloride **60-2,** which was used directly in the next step without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{24}H_{32}F_2N_3O_4$: 464.23; found: 464.35.

Step 3. Preparation of **60-3:** To a solution of **60-2** (133 mg, 0.289 mmol) and Intermediate **D11** (133 mg, 0.412 mmol) in MeCN (1.7 mL) was added HATU (157 mg, 0.412 mmol) followed by DIPEA (298 µL, 1.72 mmol) at rt under and argon atmosphere. After 1 h, the reaction mixture was concentrated *in vacuo*, and the crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford amide **60-3.** LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{38}H_{53}F_2N_4O_7$: 715.38; found: 715.55.

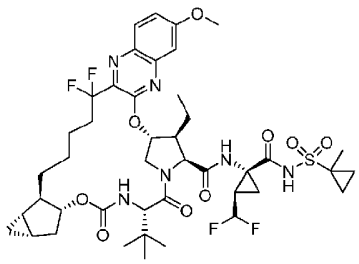
Step 4. Preparation of **60-4:** To a solution of **60-3** (188 mg, 264 µmol) in DCE (52.8 mL) was added Zhan 1 B catalyst (19.4 mg, 26.4 µmol) and the reaction mixture was degassed for 10 minutes with argon. The reaction mixture was then heated to 100 °C. After 1 h, the reaction mixture was allowed to cool to rt and was concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford macrocycle **60-4.** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{36}H_{49}F_2N_4O_7$: 687.35; found: 687.54.

Step 5. Preparation of **60-5:** To a solution of macrocycle **60-4** (119 mg, 173 µmol) in ethanol (1.0 mL) was added Pd/C (10 wt %, 18.4 mg, 17.3 µmol) at rt under an argon atmosphere. The reaction vessel was evacuated and refilled with 1 atm hydrogen gas (3 x) and the reaction mixture was stirred vigorously at rt. After 1 h, the reaction mixture was filtered through a pad of Celite with ethyl acetate washings (3 × 2 mL). The filtrate was concentrated *in vacuo* to afford macrocycle **60-5,** which was used directly in the next step without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{36}H_{51}F_2N_4O_7$: 689.36; found: 689.56.

Step 6. Preparation of **60-6:** To a solution of **60-5** (150 mg, 218 µmol) in DCM (1.1 mL) was added TMSOTf (197 µL, 1.09 mmol) at rt under an argon atmosphere. After 2 h, the reaction mixture was transferred to a solution of 0.5 N NaOH solution (5 mL) precooled to 0 °C. The resulting mixture was acidified with 1 N HCl solution to pH = 2 and was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated *in vacuo* to afford carboxylic acid **60-6,** which was used directly in the next step without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{32}H_{43}F_2N_4O_7$: 633.30; found: 633.49.

Step 7. Preparation of Example **60:** To a solution of **60-6** (100 mg, 158 µmol) and Intermediate **A9** (69.0 mg, 237 µmol) in MeCN (790 µL) was added HATU (91.5 mg, 237 µmol) followed by DIPEA (137 µL, 790 µmol) at rt under an argon atmosphere. After 3 h, the reaction mixture was concentrated *in vacuo*, was purified by preparatory HPLC (Gemini 5u C18 110Å column, 5-100% MeCN/H_2O, 0.1% trifluoroacetic acid modifier) and was lyophilized to afford Example **60** as a TFA salt. Analytic HPLC RetTime: 8.89 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{40}H_{53}F_4N_6O_9S$: 869.35; found: 859.66. ^{1}H NMR (400 MHz, CD_3OD) δ 9.29 (br s, 1 H), 7.94 (d, *J* = 9.2 Hz, 1 H), 7.31 (d, *J* = 9.2 Hz, 1 H), 7.19 (br s, 1 H), 5.87 (br s, 1 H), 5.84 (td, J_{H-F} = 55.8 Hz, J = 5.4 Hz, 1 H), 4.56 (d, J = 6.9 Hz, 1 H), 4.40 (d, J = 12.6 Hz, 1 H), 4.36 (s, 1 H), 4.17 (dd, J = 11.9, 3.4 Hz, 1 H), 3.96 (br s, 4H), 3.68 (br s, 1 H), 3.01 - 2.91 (m, 1 H), 2.71 - 2.61 (m, 1 H), 2.61 - 2.43 (m, 1 H), 2.02 (br s, 4H), 1.88 - 1.59 (m, 4H), 1.59 - 1.35 (m, 4H), 1.33 - 1.20 (m, 3H), 1.09 (s, 9H), 1.04 - 0.95 (app t, *J* = 7.0 Hz, 5H), 0.79 - 0.65 (m, 1 H), 0.49 (d, *J* = 6.5 Hz, 1 H).

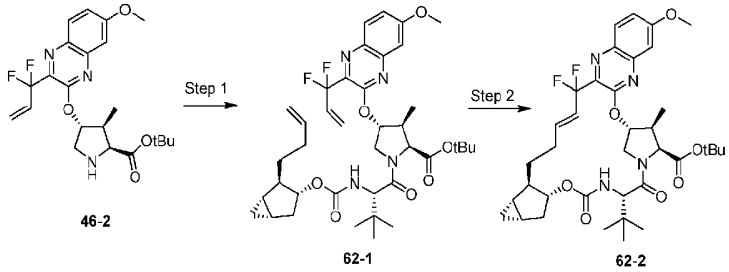
[0269] Example **61.** Preparation of (1aS,2aR,6S,9S,10S,11R,23aR,23bS)-6-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-10-ethyl-19,19-difluoro-15-methoxy-4,7-dioxo-1a,2,2a,4,5,6,7,10,11,19,20,21,22,23,23a,23b-hexadecahydro-1H,9H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19][1,10,3,6]dioxadiazacyclononade cino[11,12-b]quinoxaline-9-carboxamide.

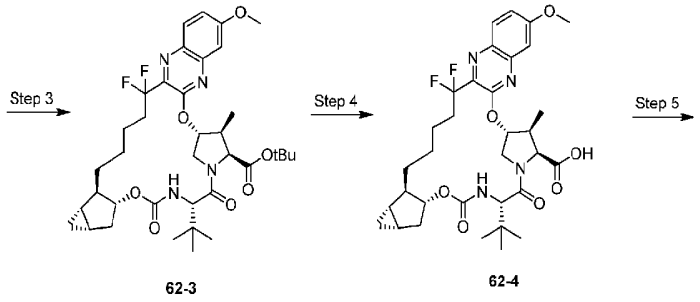


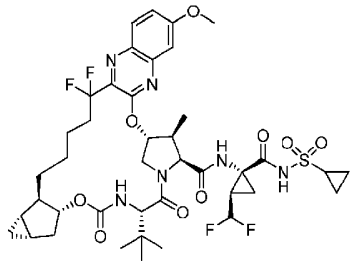
Example 61

[0270] Example **61** was prepared similarly to Example 59 substituting Intermediate **A10** for Intermediate **A9** in Step 5. The TFA salt of Example **61** was isolated. Analytic HPLC RetTime: 9.28 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{43}H_{57}F_4N_6O_9S$: 909.38; found: 909.59. ^{1}H NMR (400 MHz, CD_3OD) δ 9.28 (s, 1 H); 7.95 (d, J = 9.2 Hz, 1 H); 7.33 (dd, J = 9.2, 2.4 Hz, 1 H); 7.23 (d, J = 2.4 Hz, 1 H); 6.0 (br s, 1 H); 5.83 (br s, 1 H); 5.83 (td, J_{H-F} = 55 Hz, J = 6 Hz, 1 H); 4.94 (d, J = 7.6 Hz, 1 H); 4.61 (d, J = 7.6 Hz, 1 H); 4.34 (d, J = 7.6 Hz, 1 H); 4.32 (br s, 1 H); 4.18 (m, 1 H); 3.97 (s, 3H); 2.63-2.47 (m, 2H); 2.28-2.17 (m, 1 H); 2.12-1.96 (m, 4H); 1.83-1.26 (m, 14H); 1.53 (s, 3H); 1.19 (t, J = 7.2 Hz, 3H); 1.08 (s, 9H); 0.94-0.88 (m, 2H); 0.62-0.48 (m, 2H).

[0271] Example **62.** Preparation of (1aS,2aR,6S,9S,10S,11R,23aR,23bS)-6-tert-butyl-N-[(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-19,19-difluoro-15-methoxy-10-methyl-4,7-dioxo-1a,2,2a,4,5,6,7,10,11,19,20,21,22,23,23a,23b-hexadecahydro-1H,9H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19][1,10,3,6]dioxadiazacyclononade cino[11,12-b]quinoxaline-9-carboxamide







Example 62

Step 1. Preparation of **Example 62-1:** HATU (214 mg, 0.563 mmol, Oakwood) and DIPEA (0.30 mL, 1.72 mmol) were added to a mixture of **46-2** (186 mg, 0.428 mmol) and Intermediate **D16** (157 mg, 0.508 mmol) in 10 mL of acetonitrile under argon. After stirring overnight, the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica

gel chromatography (0-30% ethyl acetate in hexanes) to yield Intermediate **62-1.** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{39}H_{53}F_2N_4O_7$: 727.38; found: 727.51.

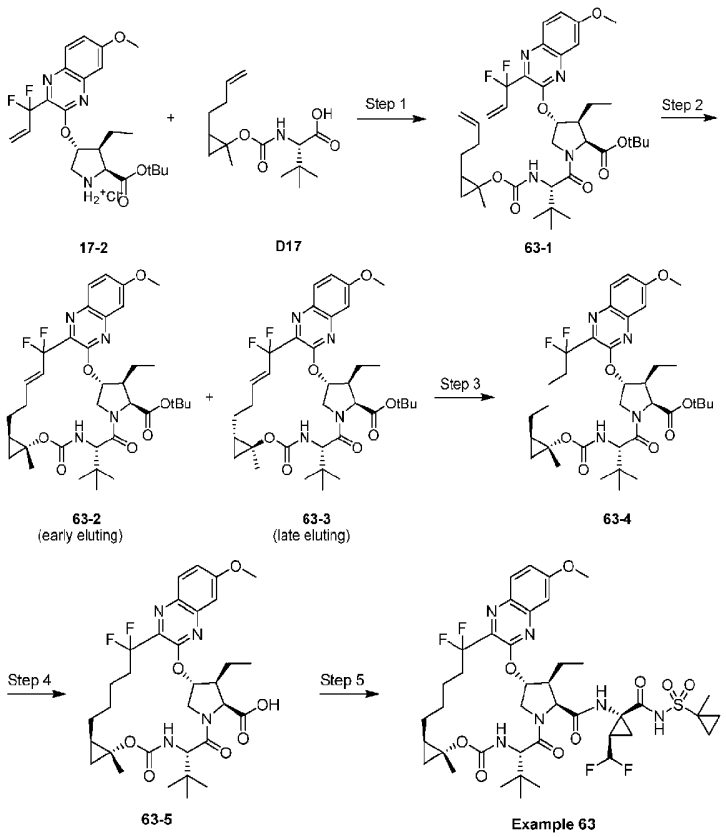
Step 2. Preparation of **62-2:** A mixture of **62-1** (275 mg, 0.378 mmol) and Zhan 1 B catalyst (34 mg, 0.046 mmol, Strem) in 75 mL of DCE was deoxygenated with argon for 17 minutes. The mixture was then heated at reflux for 80 minutes. An additional 8 mg of Zhan 1B catalyst was added and mixture stirred at reflux for twenty minutes. After cooling to room temperature, reaction mixture was concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-25% ethyl acetate in hexanes) to yield intermediate **62-2.** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{37}H_{49}F_2N_4O_7$: 699.35; found: 669.50.

Step 3. Preparation of mixture of **62-3:** Palladium on carbon (10 wt % Pd, 60 mg, 0.057 mmol) was added to a solution of **62-2** (207 mg, 0.297 mmol) in 7 mL of ethanol. The atmosphere was replaced with hydrogen and mixture was stirred overnight. The reaction was filtered over Celite, washing with ethanol. Filtrate was concentrated *in vacuo* to yield intermediate **62-3,** which was used in the next step without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{37}H_{51}F_2N_4O_7$: 701.36; found: 701.65.

Step 4. Preparation of **62-4:** TFA (1.6 mL, 20.9 mmol) was added slowly to a solution of **62-3** (202 mg, 0.289 mmol) in 4.5 mL of dichloromethane. After 3.5 hours, mixture was concentrated under reduced pressure to near dryness. Resulting residue was taken up in 30 mL of ethyl acetate, washed with 20 mL of water, 20 mL of sat. $NaHCO_{3\,(aq)}$, and separated. Aqueous layers were extracted with ethyl acetate (3 x 20 mL). Combined organics were washed with 30 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to yield intermediate **62-4,** which was used in the next step without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{33}H_{43}F_2N_4O_7$: 645.30; found: 645.53.

Step 5. Preparation of Example **62:** HATU (113 mg, 0.297 mmol, Oakwood) and DIPEA (0.17 mL, 0.978 mmol) were added to a mixture of **62-4** (120 mg, 0.186 mmol) and Intermediate **A9** (110 mg, 0.379 mmol) in 6 mL of acetonitrile under argon. After stirring for overnight, reaction mixture was taken up in 30 mL of ethyl acetate and washed with 20 mL of 1 N aqueous HCl. The aqueous layer was extracted three times with ethyl acetate. Combined organics were washed with 50% brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-50% ethyl acetate in hexanes) and reverse phase prep HPLC (50-100% acetonitrile in water, with 0.1% trifluoroacetic acid buffer) to yield the trifluoroacetic acid salt of Example **62.** Analytic HPLC RetTime: 9.03 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{41}H_{53}F_4N_6O_9S$: 881.35; found: 881.57. ^{1}H NMR (400 MHz, CD_3OD): δ 9.27 (s, 1 H), 7.94 (d, J = 8.8 Hz, 1 H), 7.33 (dd, J = 9.2, 2.8 Hz, 1 H), 7.27 (d, J = 2.8 Hz, 1 H), 5.84 (td, J_{H-F} = 56 Hz, J = 6.8 Hz, 1 H), 5.75 (d, J = 3.6 Hz, 1 H), 4.94 (d, J = 7.2 Hz, 1 H), 4.55 (d, J = 7.2 Hz, 1 H), 4.35 (d, J = 12 Hz, 1 H), 4.32 (s, 1 H), 4.22-4.16 (dd, J = 12, 4 Hz, 1 H), 3.97 (s, 3H), 3.01-2.94 (m, 1 H), 2.81-2.72 (m, 1 H), 2.66-2.40 (m, 1 H), 2.36-2.28 (m, 1 H), 2.10-1.94 (m, 4H), 1.82-1.72 (m, 2H), 1.70-1.22 (m, 10H), 1.14-1.02 (m, 7H), 1.10 (s, 9H), 0.61-0.49 (m, 2H).

[0272] Example **63.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-18,18-difluoro-14-methoxy-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide



Step 1. Preparation of **63-1:** Amine hydrochloride **17-2** (500 mg, 1.03 mmol) was combined with intermediate mixture **D17** (378.5 mg, 1.34 mmol), DIPEA (1.8 mL, 10.3 mmol) and DMF (3 mL). HATU (587.1 mg, 1.55 mmol) was then added to the reaction mixture, which was stirred at room temperature for 18 hrs. Reaction mixture was then diluted with water (20 mL) and 1 N HCl (10.5 mL) and taken up into methylene chloride (20 mL). Organics were separated and aqueous layer was extracted three times with methylene chloride (10 mL). Combined organics were then washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Crude residue was then purified via silica gel chromatography to give **63-1** as a 1:1 diastereomeric mixture. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{38}H_{53}F_2N_4O_7$: 715.4; found: 715.4.

Step 2. Preparation of **63-2** and **63-3:** Diastereomeric mixture **63-1** (496 mg, 0.695 mmol) and Zhan 1B catalyst (53.8 mg, 0.0695 mmol, Strem) were dissolved in 140 mL of anhydrous DCE and sparged with N_2 for 30 minutes. The mixture was then heated to 100 °C for 90 minutes, and an additional portion of Zhan 1 B catalyst was added (54 mg, 0.695 mmol, Strem). Reaction was then cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified via silica gel chromatography (0% to 40% ethyl acetate in hexanes) to yield single diastereomers **63-2** (early eluting fraction) and **63-3** (late eluting fraction). Early eluting fraction: LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{36}H_{49}F_2N_4O_7$: 687.4; found: 687.2. Late eluting fraction: LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{36}H_{49}F_2N_4O_7$: 687.4; found: 687.3.

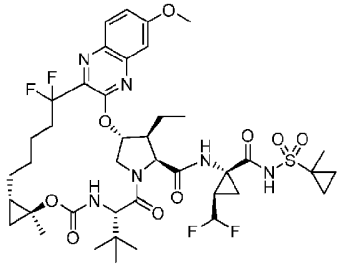
Step 3. Preparation of **63-4:** Palladium on carbon (10% w/w, 155 mg) was added to a solution of **63-2** (155 mg, 0.226 mmol) in a ethanol (3 mL). Mixture was stirred under an atmosphere of hydrogen for 1 hr and was then filtered through a plug of Celite, and washed with ethyl acetate. Filtrate was concentrated under reduced pressure to yield **63-4,** which was used in the next step without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{36}H_{51}F_2N_4O_7$: 689.4; found: 689.3.

Step 6. Preparation of **63-5:** Intermediate **63-4** (153.5 mg, 0.222 mmol) was dissolved in a mixture of 1:1 TFA:DCM (6 mL) and stirred at room temperature for 3 hrs. Reaction mixture was then concentrated *in vacuo* to give **63-5,** which was used in the subsequent step without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{32}H_{44}N_4O_7$: 633.3; found: 633.2.

Step 7. Preparation of Example **63:** HATU (99.2 mg, 0.261 mmol) and DIPEA (271 µL, 2.1 mmol) were added to a mixture of **63-5** (140.5 mg, 0.222 mmol) and **A10** (100 mg, 0.316 mmol) in 1 mL of DMF. After stirring overnight at room temperature, reaction mixture was poured into water, acidified to pH 1 with 1 N aqueous HCl, and extracted three times with methylene chloride (15 mL). Combined organics were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The

resulting residue was purified by reverse phase prep HPLC (5-100% acetonitrile in water, with 0.1% trifluoroacetic acid buffer) to afford Example **63.** Analytic HPLC RetTime: 8.951 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{41}H_{55}F_4N_6O_9S$: 883.4; found: 883.2. ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (d, *J* = 9.2 Hz, 1 H), 7.33 (dd, *J* = 9.2, 2.8 Hz, 1 H), 7.23 (d, *J* = 2.7 Hz, 1H), 6.03 (d, *J* = 3.9 Hz, 1 H), 5.80 (td, *J* = 55.8, 6.7 Hz, 1 H), 4.61 (d, *J* = 6.9 Hz, 1H), 4.46 (d, *J* = 12.2 Hz, 1H), 4.26 - 4.14 (m, 2H), 4.01 - 3.91 (m, 3H), 2.65 - 2.47 (m, 2H), 2.11 - 1.85 (m, 5H), 1.84 - 1.61 (m, 3H), 1.61 - 1.46 (m, 10H), 1.46 - 1.32 (m, 3H), 1.33 - 1.17 (m, 4H), 1.09 (d, *J* = 15.9 Hz, 10H), 1.04 - 0.95 (m, 1 H), 0.94 - 0.84 (m, 2H), 0.21 - 0.12 (m, 1 H).

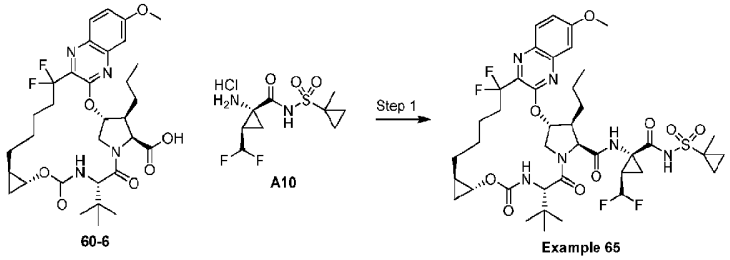
[0273] Example **64.** Preparation of (1aS,5S,8S,9S,10R,22aS)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-18,18-difluoro-14-methoxy-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide



Example 64

[0274] Example **64** was prepared in a similar fashion to Example **63,** substituting late eluting **63-3** for early eluting **63-2** in Step 3. Example **64** was then isolated. Analytic HPLC RetTime: 8.535 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{41}H_{57}F_2N_6O_9S$: 883.4; found: 883.3. ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (d, *J* = 8.9 Hz, 1 H), 7.45 - 7.16 (m, 2H), 5.97 - 5.52 (m, 2H), 4.74 (d, *J* = 7.6 Hz, 1 H), 4.50 - 4.16 (m, 1 H), 4.06 - 3.86 (m, 5H), 2.77 - 2.57 (m, 1H), 2.51 - 2.18 (m, 2H), 2.16 - 1.86 (m, 5H), 1.75 - 1.32 (m, 16H), 1.33 - 1.03 (m, 14H), 1.02 - 0.76 (m, 2H), 0.42 - -0.09 (m, 1 H).

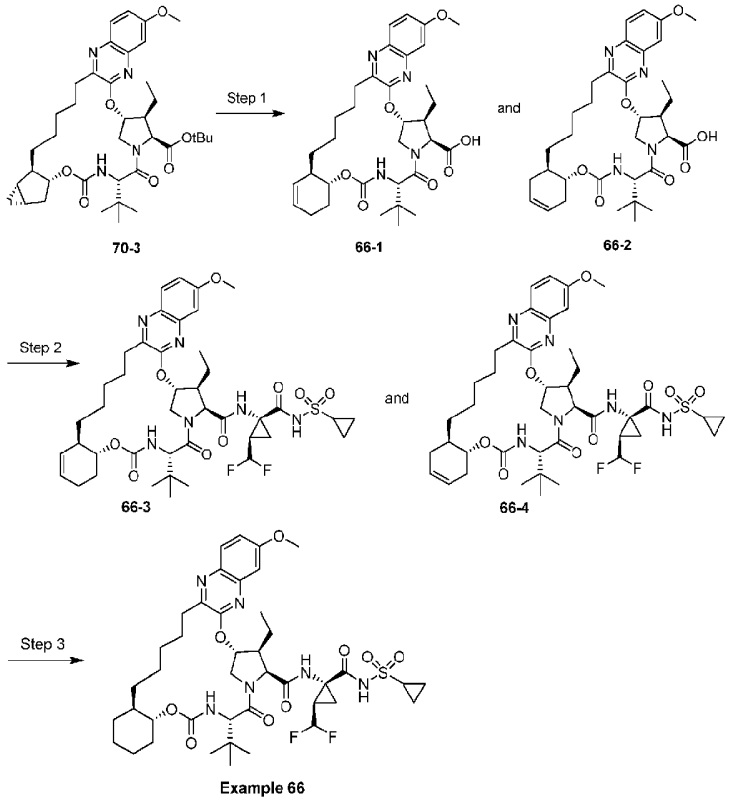
[0275] Example **65.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-18,18-difluoro-14-methoxy-3,6-dioxo-9-propyl-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide



60-6 A10 Example 65

[0276] Step 1. Preparation of Example **65:** To a solution of **60-6** (52 mg, 82 µmol) and Intermediate **A10** (37.5 mg, 123 µmol) in MeCN (411 µL) was added HATU (47.5 mg, 123 µmol) followed by DIPEA (73 µL, 411 µmol) at rt under an argon atmosphere. After 20 h, the reaction mixture was concentrated *in vacuo*, was purified by preparatory HPLC (Gemini 5u C18 110Å column, 5-100% MeCN/H_2O, 0.1% trifluoroacetic acid modifier) and was lyophilized to afford Example **65** as a TFA salt. Analytic HPLC RetTime: 8.99 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{41}H_{55}F_4N_6O_9S$: 883.36; found: 883.60. ^{1}H NMR (400 MHz, CD_3OD) δ 9.26 (s, 1 H), 7.95 (d, *J* = 9.1 Hz, 1 H), 7.33 (dd, J = 9.2, 2.8 Hz, 1 H), 7.22 (d, *J* = 2.8 Hz, 1 H), 5.89 (d, *J* = 3.2 Hz, 1 H), 5.81 (td, J_{H-F} = 55.5 Hz, J = 6.5 Hz, 1 H), 4.59 (d, *J* = 7.0 Hz, 1 H), 4.40 (d, J = 12.5 Hz, 1 H), 4.36 (s, 1 H), 4.17 (dd, J = 12.2, 3.8 Hz, 1 H), 3.97 (s, 3H), 3.73 - 3.66 (m, 1 H), 2.73 - 2.64 (m, 1 H), 2.63 - 2.45 (m, 1 H), 2.01 (br s, 3H), 1.85 - 1.62 (m, 4H), 1.62 - 1.53 (m, 3H), 1.51 (s, 3H), 1.48 - 1.22 (m, 5H), 1.08 (s, 9H), 1.01 (app t, *J* = 7.3 Hz, 4H), 0.94 - 0.87 (m, 2H), 0.80 - 0.69 (m, 1 H), 0.50 (d, *J* = 7.1 Hz, 1 H).

[0277] Example **66.** Preparation of (4aR,8S,11S,12S,13R,25aR)-8-tert-butyl-N-[(1 R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-12-ethyl-17-methoxy-6,9-dioxo-2,3,4,4a,6,7,8,9,12,13,21,22,23,24,25,25a-hexadecahydro-1H,11H-10,13-methanoquinoxalino[2,3-k][1,10,3,6]benzodioxadiazacyclononadecine-11-carboxamide.



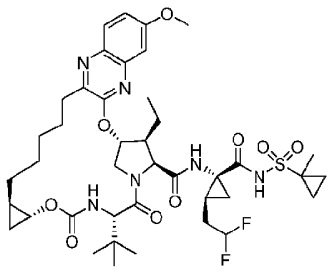
Example 66

Step 1. Preparation of **66-1** and **66-2.** To a solution of Intermediate **70-3** (283 mg, 0.42 mmol) in CH_2Cl_2 (5 mL) was added TMSOTf (380 µL, 2.1 mmol). After stirring for 2 h, the reaction mixture was poured into stirring 1 N NaOH (12 mL). The mixture was transferred to a separatoty funnel, acidified to pH 3 with 1 N HCl, extracted with CH_2Cl_2, dried over magnesium sulfate, and concentrated. The crude residue was purified by silica gel chromatography (0-10% MeOH/EtOAc) to yield a mixture of **66-1** and **66-2.** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{34}H_{47}N_4O_7$: 623.34; found: 623.66.

Step 2. Preparation of **66-3** and **66-4.** To a solution of **66-1** and **66-2** (58 mg, 0.09 mmol), intermediate **A9** (32 mg, 0.11 mmol), TBTU (42 mg, 0.13 mmol) and DMAP (16 mg, 0.14 mmol) in DMF (3 mL) was added DIPEA (47 µL, 0.27 mmol) and the reaction was stirred at rt for 23 h. The reaction was quenched with water, diluted with EtOAc, washed with sat. $NaHCO_3$, brine, dried over magnesium sulfate, and concentrated. The crude material was purified by reverse phase HPLC (Gemini, 30-85% ACN/H_2O + 0.1% TFA) and lyophilized to give the TFA salt of Intermediate **66-3** and **66-4** mixture. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{42}H_{57}F_2N_6O_9S$: 859.39; found: 859.65.

Step 3. Preparation of Example **66:** To **66-3** and **66-4** (5 mg, 0.005 mmol) that was taken up in EtOH (2 mL) and treated with Pd/C (10%, 5 mg). The atmosphere was replaced with hydrogen and stirred at rt for 2.5 h. The reaction was filtered over Celite, washed with EtOAc and concentrated. The residue was purified by silica gel chromatography (0-10% MeOH/EtOAc) and lyophilized to give the parent compound. Analytical HPLC RetTime: 9.15 min.LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{42}H_{59}F_2N_6O_9S$: 862.01; found: 862.37. ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 - 7.73 (m, 1 H), 7.25 (m, 1 H), 6.87 (d, *J* = 9.8 Hz, 1 H), 6.05 (m, 2H), 4.83 - 4.74 (m, 1 H), 4.70 (d, *J* = 7.6 Hz, 1 H), 4.52 - 4.28 (m, 2H), 4.16 (m, 2H), 4.05 - 3.86 (m, 4H), 3.86 - 3.45 (m, 4H), 3.22 - 3.00 (m, 1 H), 2.89 (s, 1 H), 2.77 - 2.55 (m, 1 H), 2.25 (t, *J* = 7.3 Hz, 1 H), 2.09 - 0.81 (m, 35H).

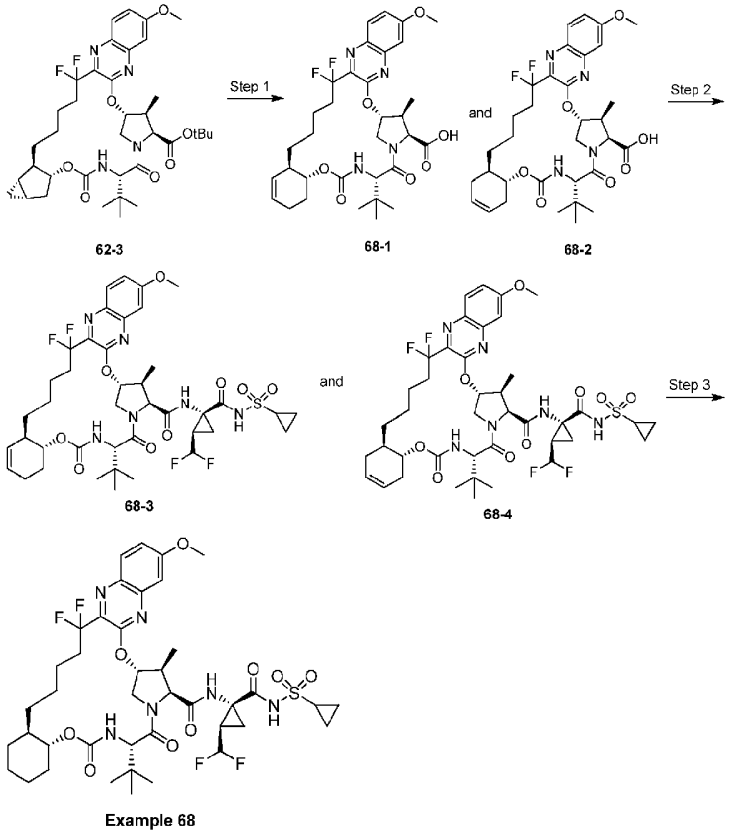
[0278] Example **67.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2S)-2-(2,2-difluoroethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 67

[0279] Example **67** was prepared similarly to Example **1** substituting Intermediate **A8** for Intermediate **A10** in Step 8. The TFA salt of Example **67** was isolated. Analytic HPLC RetTime: 8.85 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{41}H_{57}F_2N_6O_9S$: 847.99; found: 847.64. ^{1}H NMR (400 MHz, CD_3OD) δ 9.00 (s, 1 H); 7.79 (d, J = 9.2 Hz, 1 H); 7.23 (dd, J = 9.2, 2.4 Hz, 1 H); 7.15 (d, J = 2.4 Hz, 1 H); 5.89 (tt, J_{H-F} = 54 Hz, J = 4.4 Hz, 1 H); 5.89 (br s, 1 H); 4.61 (d, J = 7.2 Hz, 1 H); 4.39 (br s, 1 H); 4.37 (d, J = 9.2 Hz, 1 H); 4.16 (dd, J = 9.2 Hz, 7.2 Hz, 1 H); 3.92 (s, 3H); 3.78-3.72 (m, 1 H); 3.10-2.88 (m, 1 H); 2.86-2.74 (td, J = 12, 4.4 Hz, 1 H); 2.62-2.53 (m, 1 H); 2.18-2.04 (m, 1 H); 1.88-1.46 (m, 14H); 1.53 (s, 3H); 1.28-1.20 (m, 4H); 1.10 (s, 9H); 1.02-0.96 (m, 2H); 0.96-0.86 (m, 2H); 0.78-0.67 (m, 1H); 0.54-0.47 (m, 1H).

[0280] Example **68.** Preparation of (4aR,8S,11S,12S,13R,25aS)-8-tert-butyl-N-[(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-21,21-difluoro-17-methoxy-12-methyl-6,9-dioxo-2,3,4,4a,6,7,8,9,12,13,21,22,23,24,25,25a-hexadecahydro-1H,11H-10,13-methanoquinoxalino[2,3-k][1,10,3,6]benzodioxadiazacyclononadecine-11-carboxamide



Example 68

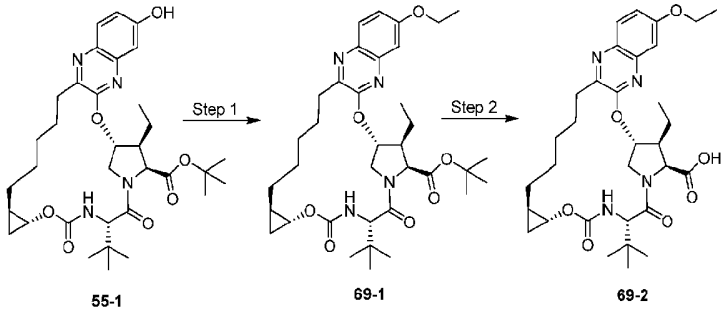
Step 1. Preparation of **68-1** and **68-2** (mixture): TMSOTf (0.6 mL, 3.3 mmol) was added to a solution of intermediate **62-3** (424 mg, 0.606 mmol) in 7 mL of dichloromethane at room temperature. After 1 hour, an additional 0.2 mL of TMSOTf was added. After a total of three hours, reaction mixture was concentrated to yield a mixture of **68-1** and **68-2** isomers, which was used in the next step without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{33}H_{43}F_2N_4O_7$: 645.30; found: 645.49.

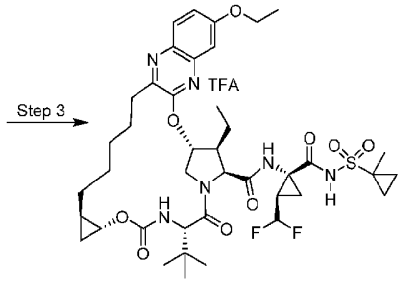
Step 2. Preparation of **68-3** and **68-4** (mixture): HATU (209 mg, 0.550 mmol, Oakwood) and DIPEA (0.25 mL, 1.43 mmol) were added to the mixture of **68-1** and **68-2** from the previous step (176 mg, 0.273 mmol) and Intermediate **A9** (161 mg, 0.555 mmol) in

4 mL of acetonitrile and 2 mL of DMF under argon. After one hour, an additional 100 mg of Intermediate **A9** was added. After two hours, reaction mixture was taken up in 30 mL of ethyl acetate and washed with 20 mL of 1 N aqueous HCl. The aqueous layer was extracted three times with ethyl acetate. Combined organics were washed with 50% brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-50% ethyl acetate in hexanes) and reverse phase prep HPLC (50-100% acetonitrile in water, with 0.1% trifluoroacetic acid buffer) to yield the trifluoroacetic acid salts of a mixture of **68-3** and **68-4.** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{41}H_{53}F_4N_6O_9S$: 881.35; found: 881.50.

Step 3. Preparation of Example **68:** Palladium on carbon (10 wt % Pd, 2 mg, 0.0019 mmol) was added to a solution of the mixture of **68-3** and **68-4** from the previous step (4.5 mg, 0.0045 mmol) in 1 mL of ethanol. The atmosphere was replaced with hydrogen and mixture was stirred for two hours. The reaction was filtered over Celite, washing with ethanol. Filtrate was concentrated *in vacuo* to yield Example **68.** Analytic HPLC RetTime: 8.81 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{41}H_{55}F_4N_6O_9S$: 883.36; found: 883.64. ^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (d, J = 10.4 Hz, 1 H), 7.34-7.30 (m, 2H), 6.13 (td, J_{H-F} = 57 Hz, J = 6.8 Hz, 1 H), 5.88-5.84 (m, 1 H), 4.62 (d, J = 7.6 Hz, 1 H), 4.38-4.30 (m, 2H), 4.20-4.05 (m, 2H), 3.98 (s, 3H), 2.87-2.76 (m, 2H), 2.34-2.16 (m, 2H), 1.92-1.54 (m, 6H), 1.46-1.36 (m, 3H), 1.34-1.12 (m, 8H), 1.20 (d, J = 7.6 Hz, 3H), 1.08-0.96 (m, 4H), 1.04 (s, 9H), 0.93-0.78 (m, 4H).

[0281] Example **69.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-14-ethoxy-9-ethyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide





Example 69

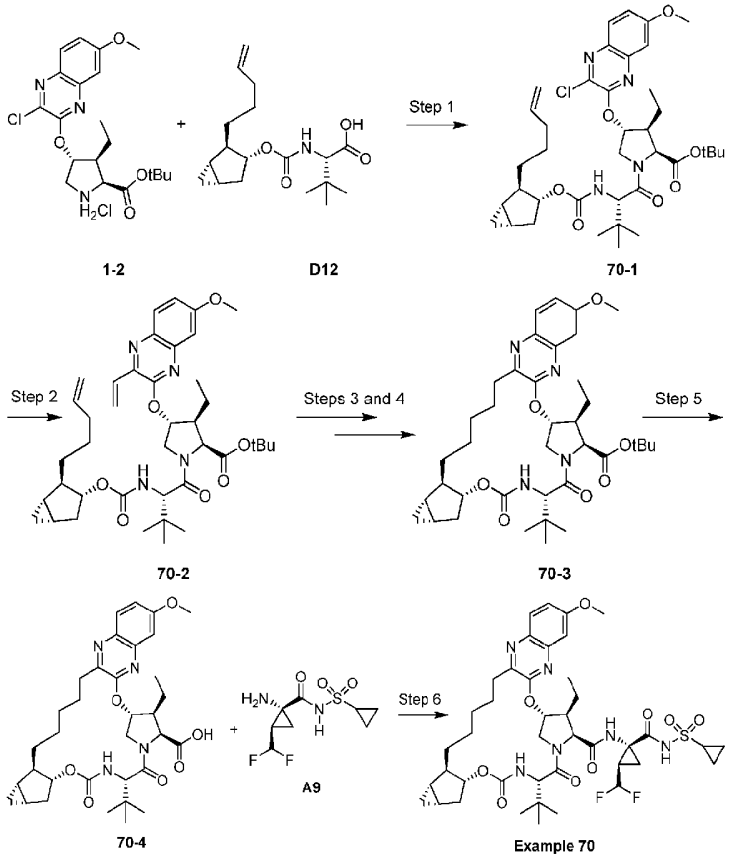
Step 1. Preparation of **69-2.** Quinoxalinol **55-1** (54 mg, 0.086 mmol) was suspended in ACN (2 mL) and treated with Cs_2CO_3 (84 mg, 0.259 mmol) and bromoethane (0.032 mL, 0.432 mmol). The reaction mixture was stirred at RT for 16 h. The reaction was filtered and the crude material was purified by flash column chromatography to afford **69-2.** LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{36}H_{52}N_4O_7$: 652.38; found: 653.41.

Step 2. Preparation of **69-3.** Intermediate **69-2** (0.086 mmol theoretical) was treated with DCM (10 mL) and TMSOTf (1.0 mL) at RT. After 1 h, the reaction was complete determined by LCMS. The reaction was concentrated under reduced pressure to afford **69-3,** which was carried on without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{32}H_{44}N_4O_7$: 596.32; found: 597.38.

Step 3. Preparation of Example **69.** Carboxcylic acid **69-3** (0.0.086 mmol theoretical) was treated with intermediate **A10** (40 mg, 0.130 mmol), TBTU (47 mg, 0.147 mmol), DMAP (18 mg, 0.147 mmol), DCM (3 mL) and DIPEA (0.075 mL, 0.432 mmol). The reaction mixture was stirred at RT for 20 h, then concentrated under reduced pressure and purified by reverse phase HPLC to

afford Example **69** as a TFA salt. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{41}H_{56}F_2N_6O_9S$: 846.38; found: 847.75.

[0282] Example **70.** Preparation of (1aS,2aR,6S,9S,10S,11R,23aR,23bS)-6-tert-butyl-N-[(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-10-ethyl-15-methoxy-4,7-dioxo-1 a,2,2a,4,5,6,7,10,11,19,20,21,22,23,23a,23b-hexadecahydro-1H,9H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19] [1,10,3,6]dioxadiazacyclononade cino[11,12-b]quinoxaline-9-carboxamide



Step 1. Preparation of **70-1:** To a solution of **1-2** (575 mg, 1.41 mmol), **D12** (410 mg, 1.26 mmol) and HATU (696 mg, 1.80 mmol) in DMF (12 mL) was added DIPEA (1.0 mL, 5.64 mmol) and the reaction was stirred at rt. After stirring for 2 h, additional HATU (350 mg, 0.92 mmol) and DIPEA (0.5 mL, 2.8 mmol) was added to the reaction, and the mixture was stirred for 14 h. The reaction was quenched with sat. $NaHCO_3$ solution and extracted with EtOAc, washed subsequently with brine, dried over magnesium sulfate and concentrated. The crude product was purified by silica gel chromatography (10-30% EtOAc/hexanes) to yield intermediate **70-1.** LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{38}H_{54}ClN_4O_7$: 713.37; found: 713.95.

Step 2. Preparation of **70-2:** To a solution of **70-1** (542 mg, 0.76 mmol), TEA (0.16 mL, 1.14 mmol) and potassium vinyltrifluoroborate (153 mg, 1.14 mmol) in EtOH (10 mL) was added PdCl2(dppf) (62 mg, 0.08 mmol). The reaction was degassed with N_2 for 10 min and heated to 80 °C for 1 h. The reaction was quenched with sat. $NaHCO_3$ solution and extracted with EtOAc, washed subsequently with brine, dried over magnesium sulfate and concentrated. The residue was purified using silica gel chromatography (0-20% EtOAc/hexanes) to give intermediate **70-2.** LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{40}H_{57}N_4O_7$: 705.42; found: 705.05.

Step 3 and 4. Preparation of **70-3:** To a solution of **70-2** (470 mg, 0.66 mmol) in DCE (100 mL) was added Zhan 1B catalyst (49 mg, 0.07 mmol) and the reaction was degassed for 30 minutes with N_2. The reaction was heated to 100 °C for 1 h, allowed to cool to rt and concentrated. The crude product was purified by silica gel chromatography to give product (358 mg; LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{38}H_{53}N_4O_7$: 677.39; found: 677.52) that was taken up in EtOH (6 mL) and EtOAc (2 mL) and treated with Pd/C (10%, 350 mg). The atmosphere was replaced with hydrogen and stirred at rt for 1.5 h. The reaction was filtered over Celite, washed with EtOAc and concentrated (358 mg intermediate **70-3**) that was used subsequently without further purification. LCMS-

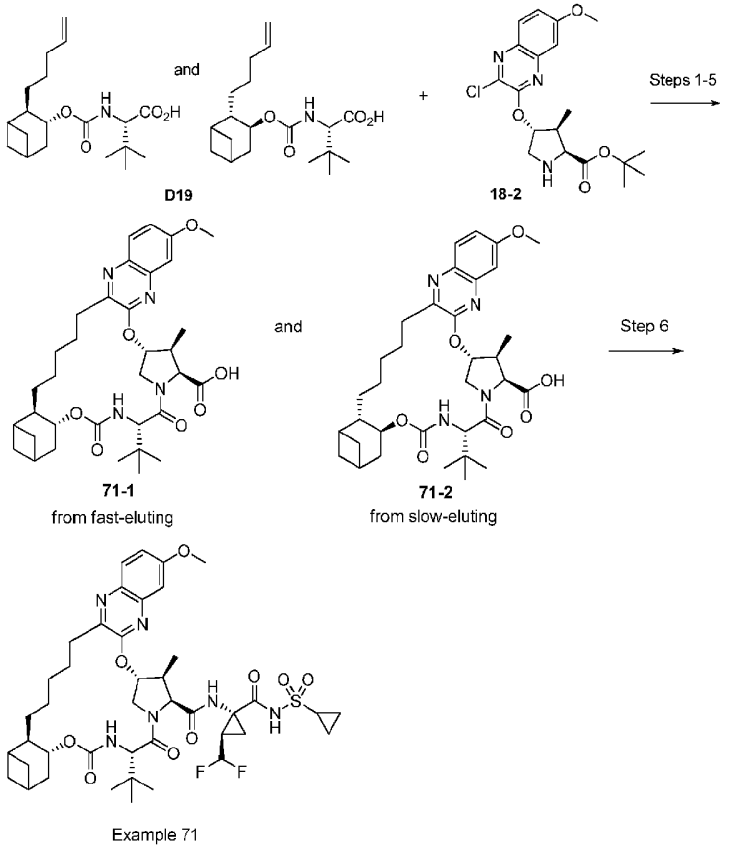
ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{38}H_{55}N_4O_7$: 679.41; found: 679.44.

Step 5. Preparation of **70-4:** To a solution of **70-3** (100 mg, 0.15 mmol) in DCM (1 mL) was added TFA (1 mL) and stirred at rt for 2 h. The reaction was diluted with EtOAc, washed with H_2O, basicified to pH 7 with sat. $NaHCO_3$ solution, dried over magnesium sulfate, and concentrated to give a residue of intermediate **70-4** that was used subsequently without further purification LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{34}H_{47}N_4O_7$: 623.34; found: 623.44 .

Step 6. Preparation of Example **70:** To a solution of **70-4** (94 mg, 0.15 mmol), intermediate **A9** (65 mg, 0.22 mmol), TBTU (87 mg, 0.27 mmol) and DMAP (27 mg, 0.22 mmol) in DCM (3 mL) was added DIPEA (0.13 mL, 0.75 mmol) and the reaction was stirred at rt for 2 h. The reaction was quenched with water, diluted with EtOAc, washed with sat. $NaHCO_3$, brine, dried over magnesium sulfate, and concentrated. The crude material was purified by reverse phase HPLC (Gemini, 30-85% ACN/H_2O + 0.1% TFA) and lyophilized to give Example **70** (23 mg) as a TFA salt.

Analytical HPLC RetTime: 9.32 min.LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{42}H_{57}F_2N_6O_9S$: 859.39; found: 859.54. ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (s, 1 H), 7.83 (d, *J* = 9.1 Hz, 1 H), 7.26 (dd, *J* = 9.1, 2.8 Hz, 1 H), 7.20 (d, *J* = 2.7 Hz, 1 H), 6.09 - 5.68 (m, 2H), 5.51 (s, 1 H), 5.07 - 4.97 (m, 1 H), 4.70 - 4.55 (m, 1 H), 4.42 - 4.29 (m, 2H), 4.22 (dd, *J* = 12.0, 4.1 Hz, 1H), 3.96 (s, 2H), 3.75 (t, *J* = 6.7 Hz, 2H), 3.02 (m, 2H), 2.93 - 2.67 (m, 1H), 2.56 (m, 1 H), 2.13 - 1.04 (m, 30H), 1.00 (d, *J* = 6.6 Hz, 1H), 0.90 (m, 3H), 0.65 - 0.46 (m, 2H).

[0283] Example **71.** Preparation of (4aR,8S,11S,12S,13R,25aR)-8-tert-butyl-N-[(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-17-methoxy-12-methyl-6,9-d ioxo-2,3,4,4a,6,7,8,9,12,13,21,22,23,24,25,25a-hexadecahydro-1H,11H-1,3:10,13-dimethanoquinoxalino[2,3-k][1,10,3,6]benzodioxadiazacyclononadecine-11-carboxamide and



Step 1: To a solution of amine **18-2** (315 mg, 0.80 mmol), DIPEA (350 µL, 2.0 mmol) and a 1:1 mixture of acids **D19** (270 mg, 0.80 mmol) in MeCN (8 mL) was added HATU (400 mg, 1.05 mmol). The resulting solution was stirred for 2.5 h at r.t., at which time it was diluted with EtOAc (50 mL) and 0.2 N aqueous HCl (30 mL). The phases were separated, and the organic phase was dried over $MgSO_4$, filtered, and concentrated to afford a crude residue. Purification by silica gel chromatography (10% to 30% EtOAc in hexanes) provided 474 mg of a colorless oil that was used directly in the next step.

Step 2: A suspension of the product from step 1 (474 mg, ca. 0.65 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (40 mg, 0.049 mmol) and potassium vinyltrifluoroborate (189 mg, 1.41 mmol) in EtOH (8 mL) was sparged with Ar for several minutes and Et_3N (200 µL, 1.4 mmol) was added. The resulting mixture was heated under Ar to 75 °C via oil bath. After stirring 2.25 h, the reaction mixture was cooled to r.t. and was diluted with EtOAc (35 mL) and half-saturated brine (20 mL). The phases were separated, and the organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue. Purification by silica gel chromatography provided a yellow oil that was used directly in the next step.

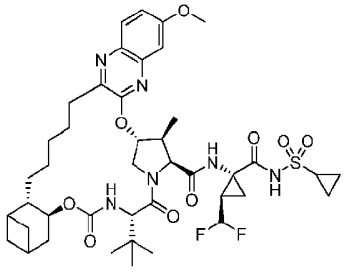
Step 3: A solution of the product from Step 3 (395 mg, 0.56 mmol) in 1,2-DCE (180 mL) was sparged with Ar for 10 min. Zhan 1B metathesis catalyst (61 mg, 0.083 mmol) was then added as a solution in DCE (4 mL), and the resulting solution was heated to 85 °C. After stirring 1.75 h, the reaction mixture was cooled to ambient temperature, concentrated onto silica gel (5 g), and purified by silica gel chromatography (10 to 15 to 25% EtOAc in hexanes) to afford 116 mg of a fast-eluting product and 84 mg of a slow-eluting product.

Step 4-5 (fast-eluting diastereomer): The fast-eluting product from Step 3 was dissolved in 1:1 EtOAc:EtOH (4 mL). Pd/C (10 wt. % Pd, 45 mg) was added, and the reaction vessel was purged twice with 1 atm H_2. The reaction mixture was stirred for 2.5 h under 1 atm H_2 and was then filtered through celite with EtOAc to afford a crude residue. This residue was dissolved in CH_2Cl_2 (1 mL) and was treated with TFA (2 mL). After stirring 2 h, the reaction mixture was concentrated in vacuo and was partitioned between EtOAc (15 mL) and 15% saturated aqueous $NaHCO_3$ (10 mL). The phases were separated, and the organic phase was washed with brine (10 mL), dried over Na_2SO_4, and filtered to provide **71-1.** LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{34}H_{47}N_4O_7$: 623.3; found: 623.2.

Step 4-5 (slow-eluting diastereomer): The slow-eluting product from Step 3 was dissolved in EtOAc (1 mL) and EtOH (7 mL). Pd/C (10 wt. % Pd, 85 mg) was added, and the reaction vessel was purged twice with 1 atm H_2. The reaction mixture was stirred for 3 h under 1 atm H_2 and was then filtered through celite with EtOAc to afford a crude residue. This residue was dissolved in CH_2Cl_2 (1 mL) and was treated with TFA (2 mL). After stirring 2 h, the reaction mixture was concentrated in vacuo and was partitioned between EtOAc (15 mL) and 15% saturated aqueous $NaHCO_3$ (10 mL). The phases were separated, and the organic phase was washed with brine (10 mL), dried over Na_2SO_4, and filtered to provide **71-2.** LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{34}H_{47}N_4O_7$: 623.3; found: 623.2.

Step 6: Preparation of Example **71:** To a suspension of acid **71-1** (49 mg, 0.079 mmol) and amine hydrochloride **A9** (41 mg, 0.14 mmol) in MeCN (1 mL) was added DIPEA (100 µL, 0.57 mmol). HATU (45 mg, 0.12 mmol) was added to the resulting solution, and the reaction was stirred at rt for 14.5 h. The reaction was then diluted with EtOAc (20 mL), 0.2 M aqueous HCl (10 mL) and brine (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue. This residue was dissolved in CH_2Cl_2 and was concentrated onto 2 g silica gel. Purification by silica gel chromatography (4% to 45% acetone in hexanes) provided an amorphous residue that was lyophilized from water and MeCN to provide Example **71.** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{42}H_{57}F_2N_6O_9S$: 859.4; found: 859.1. ^1H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1 H), 7.81 (d, *J* = 9.1 Hz, 1 H), 7.63 (s, 1H), 7.19 (dd, *J* = 9.1, 2.8 Hz, 1 H), 7.09 (d, *J* = 2.7 Hz, 1 H), 5.97 (td, *J* = 55.5, 6.9 Hz, 1H), 5.59 - 5.45 (m, 2H), 4.96 (dd, *J* = 14.4, 6.2 Hz, 1 H), 4.51 (d, *J* = 7.2 Hz, 1H), 4.42 (d, *J* = 9.8 Hz, 1 H), 4.13 (dt, *J* = 12.0, 7.7 Hz, 2H), 3.93 (s, 3H), 2.99 - 2.63 (m, 4H), 2.40 - 2.23 (m, 2H), 2.15 - 0.83 (m, 34H).

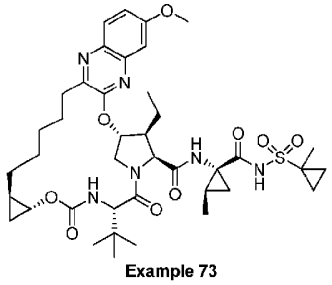
[0284] Example **72.** Preparation of (4aS,8S,11S,12S,13R,25aS)-8-tert-butyl-N-[(1 R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-17-methoxy-12-methyl-6,9-dioxo-2,3,4,4a,6,7,8,9,12,13,21,22,23,24,25,25a-hexadecahydro-1H,11H-1,3:10,13-dimethanoquinoxalino[2,3-k][1,10,3,6]benzodioxadiazacyclononadecine-11-carboxamide.



Example 72

[0285] Step 1: Preparation of Example **72:** To a suspension of acid **71-2** (49 mg, 0.079 mmol) and amine hydrochloride **A9** (38 mg, 0.13 mmol) in MeCN (1 mL) was added DIPEA (100 µL, 0.57 mmol). HATU (41 mg, 0.11 mmol) was added to the resulting solution, and the reaction was stirred at rt for 14.5 h. The reaction was then diluted with EtOAc (20 mL), 0.2 M aqueous HCl (10 mL) and brine (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a crude residue. This residue was dissolved in CH_2Cl_2 and was concentrated onto 2 g silica gel. Purification by silica gel chromatography (4% to 45% acetone in hexanes) provided an amorphous residue that was lyophilized from water and MeCN to provide Example **72.** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{42}H_{57}F_2N_6O_9S$: 859.4; found: 859.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1 H), 9.36 (s, 1 H), 7.86 (d, *J* = 9.1 Hz, 1H), 7.28 (d, *J* = 2.7 Hz, 1 H), 7.25 - 7.17 (m, 2H), 5.98 - 5.88 (m, 1 H), 5.69 (td, *J* = 55.4, 6.9 Hz, 1 H), 4.81 - 4.69 (m, 1H), 4.68 - 4.56 (m, 2H), 4.33 (d, *J* = 10.1 Hz, 1H), 3.99 (s, 3H), 3.35 (dd, *J* = 9.7, 7.0 Hz, 1 H), 3.24 - 3.13 (m, 1H), 2.97 - 2.87 (m, 1H), 2.87 - 2.72 (m, 2H), 2.57 - 2.45 (m, 1 H), 2.38 - 2.28 (m, 1H), 2.17 - 0.71 (m, 34H).

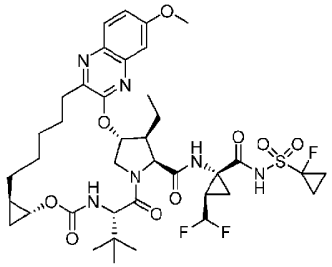
[0286] Example **73.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-9-ethyl-14-methoxy-N-[(1R,2R)-2-methyl-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 73

[0287] Example **73** was prepared similarly to Example **1** substituting Intermediate **A11** for Intermediate **A10** in Step 8. The TFA salt of Example **73** was isolated. Analytic HPLC RetTime: 8.72 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{40}H_{57}N_6O_9S$: 797.98; found: 797.54. ^{1}H NMR (400 MHz, CD_3OD) δ 8.84 (s, 1 H); 7.79 (d, J = 9.2 Hz, 1 H); 7.22 (dd, J = 9.2, 2.4 Hz, 1 H); 7.13 (d, J = 2.4 Hz, 1 H); 5.87 (d, J = 3.2 Hz, 1 H); 4.57 (d, J = 7.2 Hz, 1 H); 4.39 (br s, 1 H); 4.37 (br d, J = 10 Hz, 1H); 4.15 (dd, J = 12, 4 Hz, 1H); 3.92 (s, 3H); 3.74 (m, 1H); 3.10-2.88 (m, 1 H); 2.80 (td, J =12.4, 4 Hz, 1 H); 2.58 (m, 1 H); 1.89-1.66 (m, 3H); 1.66-1.38 (m, 11H); 1.52 (s, 3H); 1.23 (t, J =7.2 Hz, 3H); 1.16 (d, J = 6 Hz, 3H); 1.10 (s, 9H); 1.02-0.84 (m, 4H); 0.78-0.66 (m, 1 H); 0.55-0.20 (m, 1 H).

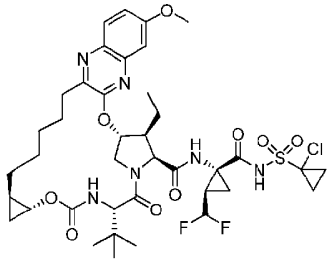
[0288] Example **74.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-fluorocyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 74

[0289] Example **74** was prepared similarly to Example 1 substituting Intermediate **A12** for Intermediate **A10** in Step 8. The TFA salt of Example **74** was isolated. Analytic HPLC RetTime: 8.81 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{39}H_{52}F_3N_6O_9S$: 837.35; found: 837.54. ^{1}H NMR (400 MHz, CD_3OD) δ 9.26 (s, 1 H); 7.79 (d, J = 9.2 Hz, 1 H); 7.22 (dd, J = 9.2, 2.4 Hz, 1 H); 7.14 (d, J = 2.4 Hz, 1 H); 5.89 (d, J = 3.6 Hz, 1 H); 5.82 (td, J_{H-F} = 56 Hz, J = 6.4 Hz, 1 H); 4.56, (d, J = 7.2 Hz, 1 H); 4.39 (s, 1 H); 4.38 (d, J = 12 Hz, 1 H); 4.16 (dd, J = 12, 7.2 Hz, 1 H); 3.92 (s, 3H); 3.78-3.72 (m, 1 H); 3.10-2.89 (m, 1 H); 2.80 (td, J = 12, 4 Hz, 1 H); 2.63-2.54 (m, 1 H); 2.02 (m, 2H); 1.95-1.66 (m, 3H); 1.66-1.36 (m, 9H); 1.22 (t, J =7.2 Hz, 3H); 1.14-1.04 (m, 2H); 1.09 (s, 9H); 1.04-0.92 (m, 2H); 0.78-0.68 (m, 1H); 0.57-0.46 (m, 1H).

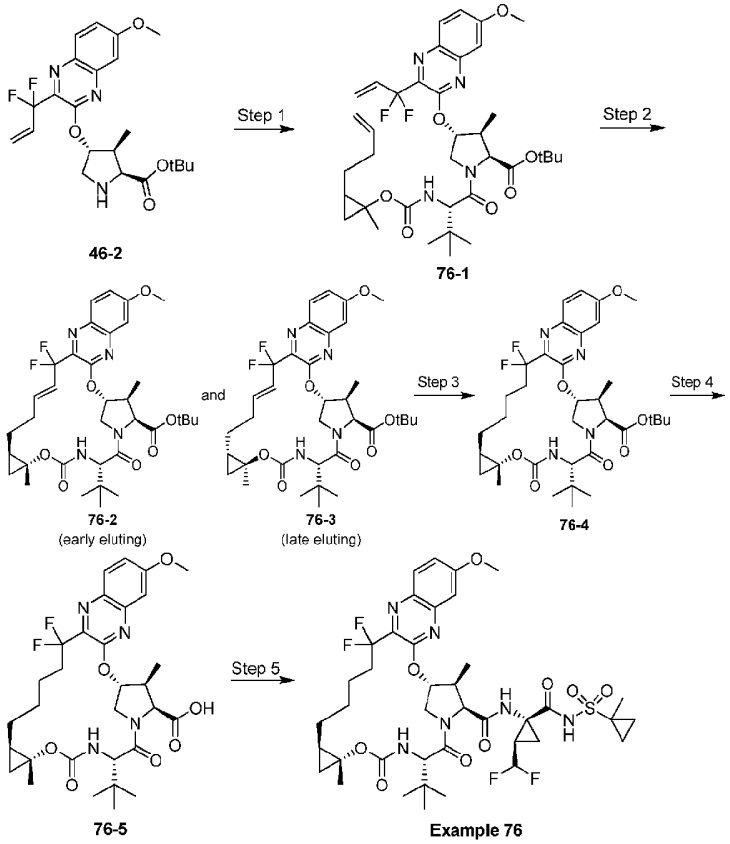
[0290] Example **75.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-1-{[(1-chlorocyclopropyl)sulfonyl]carbamoyl}-2-(difluoromethyl)cyclopropyl]-9-ethyl-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 75

[0291] Example **75** was prepared similarly to Example **1** substituting Intermediate **A13** for Intermediate **A10** in Step 8. The TFA salt of Example **75** was isolated. Analytic HPLC RetTime: 8.89 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{39}H_{52}ClF_2N_6O_9S$: 853.32; found: 853.94. ^{1}H NMR (400 MHz, CD_3OD) δ 9.24 (s, 1 H); 7.79 (d, J = 9.2 Hz, 1 H); 7.22 (dd, J = 9.2, 2.4 Hz, 1 H); 7.13 (d, J = 2.4 Hz, 1 H); 5.88 (d, J = 3.2 Hz, 1 H); 5.84 (td, J_{H-F} = 55.6 Hz, J = 6.8 Hz, 1 H); 4.57 (d, J = 7.2 Hz, 1H);4.39(brs, 1H);4.38(d,J=12Hz, 1H);4.16(dd,J=12,7.2Hz, 1 H); 3.92 (s, 3H); 3.77-3.73 (m, 1 H); 3.00-2.88 (m ,1 H); 2.86-2.75 (m, 1 H); 2.64-2.54 (m, 1 H); 2.10-1.90 (m, 4H); 1.90-1.37 (m, 12H); 1.23 (t, J = 7.2 Hz, 3H); 1.10 (s, 9H); 1.02-0.96 (m, 2H); 0.78-0.64 (m, 1 H); 0.56-0.45 (m, 1 H).

[0292] Example **76.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-18,18-difluoro-14-methoxy-1a,9-dimethyl-3,6-dioxo-1,a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Step 1. Preparation of **76-1:** HATU (502 mg, 1.32 mmol, Oakwood) and DIPEA (0.70 mL, 4.02 mmol) were added to a mixture of **46-2** (434 mg, 0.998 mmol) and Intermediate **D17** (350 mg, 1.24 mmol) in 16 mL of acetonitrile under argon. After stirring

overnight, the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (0-25% ethyl acetate in hexanes) to yield **76-1.** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{37}H_{51}F_2N_4O_7$: 701.36; found: 701.57.

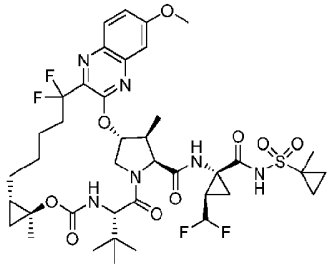
Step 2. Preparation of **76-2** and **76-3:** A diastereomeric mixture **76-1** (550 mg, 0.786 mmol) and Zhan 1B catalyst (69 mg, 0.094 mmol, Strem) in 157 mL of DCE was deoxygenated under argon for 25 minutes. The mixture was then heated at reflux for 90 minutes. An additional 35 mg of Zhan 1B catalyst was added and reaction mixture was heated at reflux for 45 minutes. After cooling to room temperature, reaction mixture was concentrated *in vacuo.* The resulting residue was purified by silica gel chromatography (0-35% ethyl acetate in hexanes) to yield single diastereomers **76-2** (early eluting component) as a white solid film and **76-3** (late eluting component) as a brown solid film. Early eluting **76-2:** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{35}H_{47}F_2N_4O_7$: 673.33; found: 673.45. Late eluting **76-3:** LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{35}H_{47}F_2N_4O_7$: 673.33; found: 673.47.

Step 3. Preparation of **76-4:** Palladium on carbon (10 wt % Pd, 51 mg, 0.048 mmol) was added to a solution of **76-2** (175 mg, 0.260 mmol) in 9 mL of ethanol. The atmosphere was replaced with hydrogen and the reaction stirred overnight. The reaction mixture was filtered over Celite and washed with ethanol. Filtrate was concentrated *in vacuo* to yield **76-4,** which was used in the next step without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{35}H_{49}F_2N_4O_7$: 675.35; found: 675.53.

Step 4. Preparation of **76-5:** TFA (1.2 mL, 15.6 mmol) was added slowly to a solution of **76-4** (155 mg, 0.230 mmol) in 3.4 mL of dichloromethane. After 4 hours, mixture was concentrated under reduced pressure to near dryness. Resulting residue was taken up in 25 mL of ethyl acetate, washed with 15 mL of water, 15 mL of sat. $NaHCO_{3\,(aq)}$, and separated. Aqueous layers were extracted with ethyl acetate (3 x 20 mL). Combined organics were washed with 30 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to yield **76-5,** which was used in the next step without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{31}H_{41}F_2N_4O_7$: 619.29; found: 619.44.

Step 5. Preparation of Example **76:** HATU (160 mg, 0.421 mmol) and DIPEA (0.20 mL, 1.15 mmol) were added to a mixture of **76-5** (140 mg, 0.226 mmol) and Intermediate **A10** (139 mg, 0.457 mmol) in 7.5 mL of MeCN under argon. After stirring for overnight, reaction mixture was taken up in 30 mL of ethyl acetate and washed with 20 mL of 1 N aqueous HCl. Layers were separated and aqueous was extracted three times with ethyl acetate. Combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo.* The resulting residue was purified by silica gel chromatography (0-45% ethyl acetate in hexanes) and reverse phase prep HPLC (50-100% acetonitrile in water, with 0.1% trifluoroacetic acid buffer) to yield the trifluoroacetic acid salt of Example **76** (Analytic HPLC RetTime: 8.80 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{40}H_{53}F_4N_6O_9S$: 869.35; found: 869.59. ^{1}H NMR (400 MHz, CD_3OD): 9.19 (s, 1 H), 7.94 (d, J = 9.2 Hz, 1 H), 7.32 (dd, J = 9.2, 2.8 Hz, 1 H), 7.27 (d, J = 2.8 Hz, 1 H), 5.78 (td, J_{H-F} = 56 Hz, J = 7.2 Hz, 1 H), 5.76-5.74 (m, 1 H), 4.56 (d, J = 6.4 Hz, 1 H), 4.48 (d, J = 12 Hz, 1 H), 4.27-4.19 (m, 1 H), 4.22 (s, 1 H), 3.97 (s, 3H), 2.76-2.70 (m, 1 H), 2.62-2.43 (m, 1 H), 2.14-1.94 (m, 3H), 1.90-1.80 (m, 1 H), 1.80-1.62 (m, 3H), 1.56-1.52 (m, 2H), 1.51 (s, 3H), 1.49 (s, 3H), 1.41-1.36 (m, 1 H), 1.27-1.18 (m, 1 H), 1.11 (s, 9H), 1.09-1.04 (m, 5H), 1.03-0.94 (m, 2H), 0.87-0.81 (m, 3H), 0.17-0.12 (m, 1 H).

[0293] Example **77.** Preparation of (1aS,5S,8S,9S,10R,22aS)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-18,18-difluoro-14-methoxy-1a,9-dimethyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.

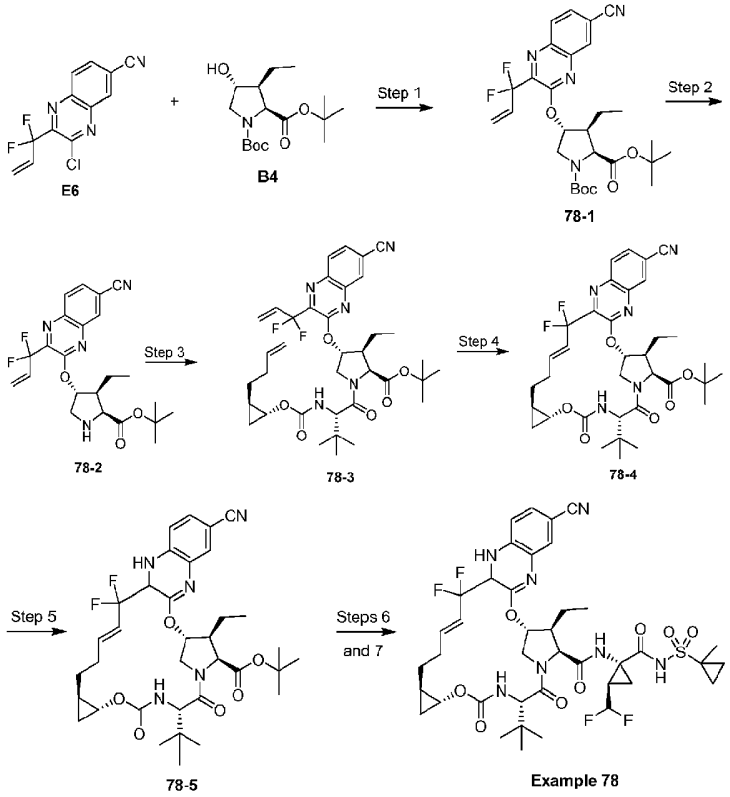


Example 77

[0294] Example **77** was prepared in a similar fashion to Example **76,** substituting late eluting **76-3** for early eluting **76-2** in step 3.

Example **76** was then isolated. Analytic HPLC RetTime: 8.46 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{40}H_{53}F_4N_6O_9S$: 869.35; found: 869.53. ^{1}H NMR (400 MHz, CD_3OD): 7.95 (d, J = 8.8 Hz, 1 H), 7.32 (d, J = 8.8 Hz, 1 H), 7.28 (s, 1 H), 6.58-6.54 (m, 1 H), 5.75 (td, J_{H-F} = 55 Hz, J = 6.8 Hz, 1 H), 5.54-5.50 (m, 1 H), 4.65 (d, J = 6.8 Hz, 1 H), 4.46 (d, J = 12.8 Hz, 1 H), 4.26-4.18 (m, 1 H), 3.97 (s, 3H), 2.92-2.71 (m, 1 H), 2.50-1.94 (m, 6H), 1.68-1.57 (m, 2H), 1.56-1.52 (m, 2H), 1.51 (s, 3H), 1,50-1.47 (m, 1 H), 1.46-1.38 (m, 3H), 1.44 (s, 3H), 1.27-1.18 (m, 2H), 1.17-1.01 (m, 3H), 1.09 (s, 9H), 0.94-0.82 (m, 4H), 0.17-0.12 (m, 1 H).

[0295] Example **78.** Preparation of (1aR,5S,8S,9S,10R,19E,22aR)-5-tert-butyl-14-cyano-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-18,18-difluoro-3,6-dioxo-1,1a,3,4,5,6,9,10,17,17a,18,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



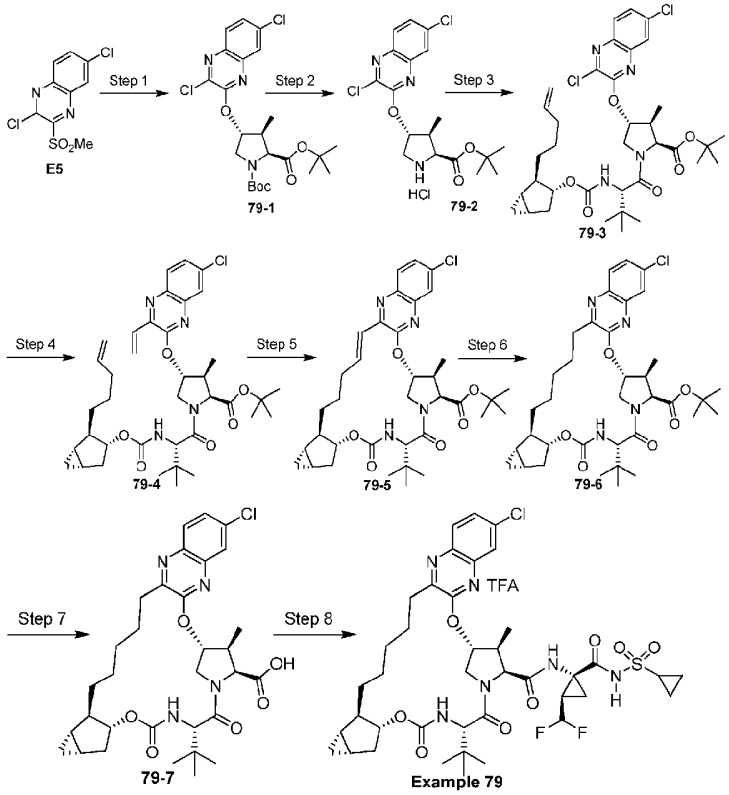
Steps 1-4. Intermediate **78-4** was prepared similarly to Intermediate **17-4,** using **E6** in place of **E3.**

Step 5: To a solution of **78-4** (90 mg, 0.135 mmol) in EtOH (0.7 mL) was added $NaBH_4$ (21 mg, 0.54 mmol). The reaction mixture was stirred at rt for 1 h. After which time the reaction mixture was filtered through a pad of celite and concentrated to give intermediate **78-5,** which was used subsequently without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for C35H45F2N5O6 : 669.76; found: 669.73.

Steps 6 and 7: Preparation of **Example 78:** To a solution of **78-5** (35 mg, 0.31 mmol) in DCM (0.4 mL), TFA (0.2 mL) was added and the mixture was stirred at 20 °C for 3 h. Solvents were removed *in vacuo* to afford a residue was used subsequently without further purification. To a suspension of this residue (33 mg, 0.05 mmol) and Intermediate **A10** (27 mg, 0.1 mmol) in DCM (0.3 mL) was added TBTU (26 mg, 0.08 mmol) and DIPEA (35 µL, 0.2 mmol) at rt. After 1 h, the solution was directly purified by reverse phase HPLC (Gemini 5u C18 110A column, 50-100% ACN/H_2O + 0.1% TFA) and lyophilized to afford the TFA salt of Example **78.** Analytical HPLC RetTime: 7.994 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for C40H49F4N7O8S: 863.92; found: 864.20.. ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 (s, 1H), 7.29 (d,1 H), 7.18 (dd,1 H), 6.64 (d, 1 H), 6.01-5.82 (m, 2H), 5.41 (m, 2H), 4.57 - 4.07 (m, 5H), 3.52 (m, 1 H), 2.55-2.28 (m, 2H), 2.06 - 1.98 (m, 2H), 1.85 (m, 1 H), 1.69 - 1.37 (m, 9H), 1.33 (m, 2H), 1.06-0.87 (m, 16H), 0.70 (m, 2H)., 0.49 (m, 1 H).

[0296] Example **79.** Preparation of (1aS,2aR,6S,9S,10S,11R,23aR,23bS)-6-tert-butyl-15-chloro-N-[(1 R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-10-methyl-4,7-dioxo-1 a,2,2a,4,5,6,7,10,11,19,20,21,22,23,23a,23b-hexadecahydro-1H,9H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19]

[1,10,3,6]dioxadiazacyclononade cino[11,12-b]quinoxaline-9-carboxamide.



Step 1. Preparation of **79-1.** Sulfonyl quinoxaline **E5** (920 mg, 3.32 mmol) was suspended in MeCN (17 mL), then treated with intermediate **B1** (1.00 g, 3.32 mmol) and Cs_2CO_3. After 17 h, the reaction mixture was filtered over celite and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (10% to 30% EtOAc/Hex) to afford ether **79-1.** LCMS-ESI$^+$ (*m/z*): [M-Boc+2H]$^+$ calcd for $C_{18}H_{22}Cl_2N_3O_3$: 398.10; found: 398.12.

Step 2. Preparation of **79-2.** *tert*-Butyl carbamate **79-1** (513 mg, 1.03 mmol) was dissolved in DCM (10 mL) and treated with HCl (4.0 mL in dioxane, 5 mL, 20 mmol). The reaction mixture was stirred at RT for 1.5 h, then concentrated under reduced pressure to afford amine hydrochloride **79-2,** which was carried on without purification. LCMS-ESI$^+$ (m/z): [M+H]$^+$calcd for $C_{18}H_{22}Cl_2N_3O_3$: 398.10; found: 398.16.

Step 3. Preparation of **79-3.** Amine hydrochloride **79-2** (1.03 mmol theoretical) and intermediate **D12** (336 mg, 1.04 mmol) were combined and treated with BEP (285 mg, 1.04 mmol), EtOAc (9 mL), NMP (1 mL) and DIPEA (0.90 mL, 5.2 mmol). The reaction mixture was stirred at 50 °C for 3 h, then cooled to RT. After an additional 15 h, the reaction mixture was diluted with EtOAc. The organic solution was washed with saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (10% to 25% EtOAc/Hex) to afford amide **79-3.** LCMS-ESI$^+$ (m/z): [M+H]$^+$calcd for $C_{36}H_{49}Cl_2N_4O_6$: 703.30; found: 703.91.

Step 4. Preparation of **79-4.** Chloro quinoxaline **79-3** (541 mg, 0.769 mmol) was treated with potassium vinyltrifluoroborate (154 mg, 1.15 mmol), Pd(dppf)Cl_2 dichloromethane adduct (63 mg, 0.077 mmol), EtOH (8 mL) and triethylamine (0.16 mL, 1.15 mmol). The stirred mixture was heated to reflux for 1 h, then cooled to RT and diluted with EtOAc. The organic solution was washed with saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (10% to 30% EtOAc/Hex) to afford vinyl quinoxaline **79-4.** LCMS-ESI$^+$ (m/z): [M+H]$^+$calcd for $C_{38}H_{52}ClN_4O_6$: 695.36; found: 695.10.

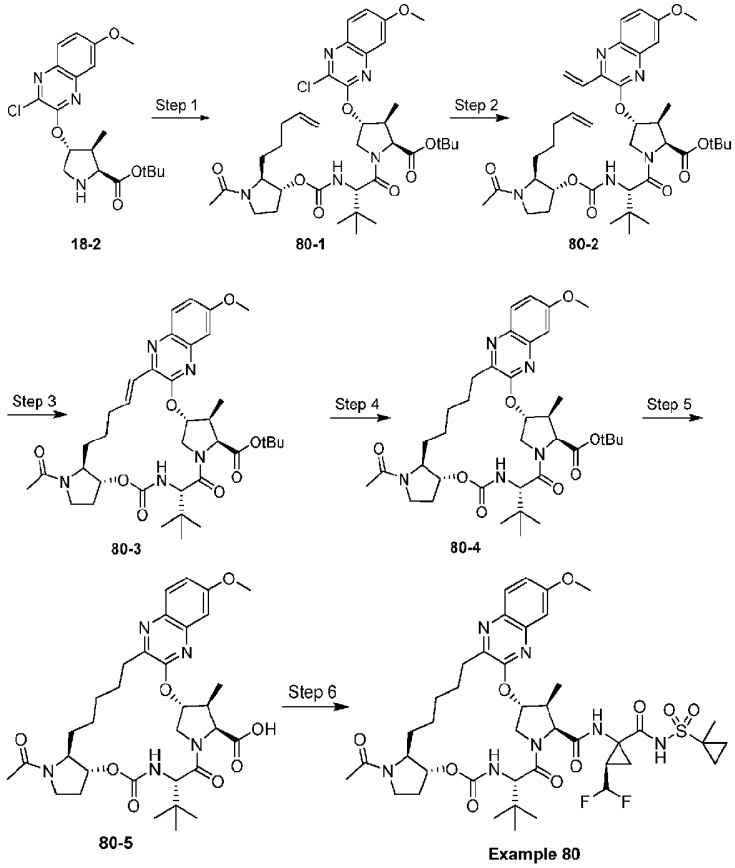
Step 5. Preparation of **79-5.** Vinyl quinoxaline **79-4** (390 mg, 0.561 mmol) was treated with DCE (112 mL) and Zhan-B catalyst (38 mg, 0.0561 mmol). The stirred mixture was degassed with bubbling N_2 for 25 min, then heated to reflux under an Ar atmosphere. After 1.5 h, the mixture was cooled to RT and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (10% to 30% EtOAc/Hex) to afford macrocycle **79-5 .** LCMS-ESI$^+$ (m/z): [M+H]$^+$calcd for $C_{36}H_{48}ClN_4O_6$: 667.33; found: 667.86.

Step 6. Preparation of **79-6.** Macrocycle **79-5** (198 mg, 0.297 mmol) was treated with EtOAc (100 mL) and 5% Rh/alumina (100 mg). H_2 gas was bubbled through the solution for 1 min and the reaction mixture was stirred at RT under an atmosphere of H_2. After 45 min, more 5% Rh/alumina (200 mg) was added. Again, H_2 gas was bubbled through the solution for 1 min and the reaction mixture was stirred at RT under an atmosphere of H_2. After another 1 h, the reaction mixture was filtered over celite and concentrated under reduced pressure. The material **(79-6)** was carried on without purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{36}H_{50}ClN_4O_6$: 669.34; found: 669.63.

Step 7. Preparation of **79-7.** Macrocycle **79-6** (0.297 mmol theoretical) was treated with DCM (10 mL) and TFA (10 mL). The reaction mixture was stirred at RT for 14 h, then concentrated under reduced pressure. The crude residue was dissolved in EtOAc and the organic solution was washed with saturated aqueous $NaHCO_3$ and 1 M citric acid. Brine was added after the citric acid wash to break up the emulsion that formed. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (100% EtOAc) to afford impure **79-7** that was carried on without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{32}H_{42}ClN_4O_6$: 613.28; found: 613.22.

Step 8. Preparation of Example **79.** Carboxcylic acid **79-7** (0.264 mmol theoretical) was treated with intermediate **A9** (156 mg, 0.537 mmol), TBTU (170 mg, 0.528 mmol), DMAP (65 mg, 0.528 mmol), DCM (2 mL) and DIPEA (0.23 mL, 1.3 mmol). The reaction mixture was stirred at RT for 19 h then concentrated under reduced pressure. The crude residue was purified by reverse phase HPLC to afford Example **79** as a TFA salt. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{40}H_{52}ClF_2N_6O_8S$: 849.32; found: 849.16. ^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (s, 1 H), 7.86 (t, *J* = 8.1 Hz, 1 H), 7.77 (t, *J* = 3.5 Hz, 1 H), 7.55 (dd, *J* = 8.8, 2.3 Hz, 1 H), 5.84 (td, *J* = 55.7, 6.7 Hz, 1 H), 5.62 (d, *J* = 3.5 Hz, 1 H), 4.98 (t, *J* = 10.6 Hz, 1 H), 4.53 (t, *J* = 9.3 Hz, 1 H), 4.42 - 4.26 (m, 2H), 4.19 (dd, *J* = 12.0, 3.9 Hz, 1 H), 3.34 (d, *J* = 7.6 Hz, 1 H), 2.99 (tt, *J* = 8.2, 4.8 Hz, 2H), 2.78 (ddt, *J* = 21.6, 14.2, 5.7 Hz, 2H), 2.28 - 2.12 (m, 1 H), 2.08 - 1.16 (m, 19H), 1.16 - 0.96 (m, 17H), 0.58 (dd, *J* = 8.3, 4.1 Hz, 1H), 0.55 - 0.44 (m, 1 H).

[0297] Example **80**. Preparation of (3aR,7S,10S,11S,12R)-1-acetyl-7-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-16-methoxy-11-methyl-5,8-dioxo-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10h-9,12-methanopyrrolo[2',3':18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide



Step 1. Preparation of **80-1:** Amine **18-2** (195 mg, 0.495 mmol) and Intermediate **D18** (192.8 mg, 0.544 mmol) were dissolved in DMF (10 mL). DIPEA (430 µL, 2.48 mmol) was added followed by HATU (207 mg, 0.544 mmol) at room temperature. After 1.5 h, the reaction mixture was concentrated in vacuo and the crude residue was directly purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford **80-1** (2:1 diastereomeric ratio favoring desired). LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{37}H_{53}ClN_5O_8$: 730.3; found: 730.48.

Step 2. Preparation of **80-2:** A stirred heterogeneous mixture of **80-1** (314 mg, 0.431 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (35.2 mg, 0.043 mmol) and potassium vinyltrifluoroborate (86.6 mg, 0.646 mmol) in EtOH (2.2 mL) was sparged with argon for 15 min. Triethylamine (320 µL, 2.3 mmol) was added and the mixture was heated to 80 °C. After 40 min, the reaction mixture was cooled to ambient temperature and was diluted with toluene (5 mL). The resulting mixture was concentrated and the crude residue was directly purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford **80-2** (2:1 diastereomeric ratio favoring desired). LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{39}H_{56}N_5O_8$: 722.4; found: 722.54.

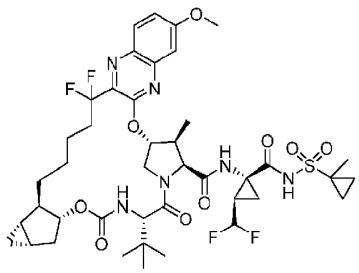
Step 3. Preparation of **80-3: 80-2** (228 mg, 0.320 mmol) was dissolved in DCE (64 mL) and the solution was sparged with Ar for 15 min. Zhan 1B catalyst (23 mg, 0.032 mmol) was added and the resulting solution was stirred at 100 °C under Ar. After 45 min, the reaction mixture was cooled to rt, was concentrated *in vacuo* and was directly purified by silica gel chromatography (0-100% ethyl acetate/hexanes gradient) to afford **80-3** (5:2 diastereomeric ratio favoring desired). LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{37}H_{52}N_5O_8$: 694.37; found: 694.53.

Step 4: Preparation of **80-4:** Olefin **80-3** (164 mg, 0.237 mmol) was dissolved in ethanol (1.19 mL) and the reaction vessel was purged with Ar. Pd/C (10 wt % Pd, 25 mg) was added in a single portion and the reaction vessel was purged thrice with H_2. The reaction was stirred at rt under 1 atm H_2 for 2 h and was diluted with ethyl acetate (10 mL). The resulting mixture was filtered through a pad of Celite and concentrated to afford a crude residue of **80-4** (5:2 diastereomeric ratio favoring desired) that was used without further purification (LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{37}H_{54}N_5O_8$: 696.39; found: 696.56.

Step 5. Preparation of **80-5:** To a solution of **80-4** (164 mg, 240 µmol) in DCM (1.2 mL) was added TFA (0.45 mL) at rt. After 7 h, the reaction mixture was diluted with ethyl acetate (50 mL) and the resulting mixture was extracted with 1 N aqueous sodium hydroxide solution (40 mL). The aqueous layer was then slowly acidified to pH=3 with concentrated hydrochloric acid, and was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated *in vacuo*. The residue was azeotropically dried with toluene (3 × 5 mL) to afford **80-5** (5:2 diastereomeric ratio favoring desired) that was used without further purification. LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{33}H_{46}N_5O_8$: 640.33; found: 640.48.

Step 6. Preparation of Example **80:** To a solution of **80-5** (140 mg, 219 µmol) and Intermediate **A10** (133 mg, 438 µmol) in MeCN (1.1 mL) was added HATU (169 mg, 438 µmol) followed by DIPEA (190 µL, 1.09 mmol) at rt under an argon atmosphere. After 15 h, the reaction mixture was concentrated *in vacuo*, was purified by preparatory HPLC (Gemini 5u C18 110Å column, 5-100% MeCN/H_2O, 0.1% trifluoroacetic acid modifier) and was lyophilized to afford Example **80** (5:2 diastereomeric ratio favoring desired) as a light yellow solid TFA salt. Analytic HPLC RetTime: 7.91 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{42}H_{58}F_2N_7O_{10}S$: 890.39; found: 890.64. ^{1}H NMR (400 MHz, CD_3OD, Minor diastereomer denoted by*) δ 9.18 (s, 1 H), 9.14 (s, 1H*), 7.78 (br d, *J* = 9.0 Hz, 1H, 1H*), 7.21 (br d, *J* = 9.0 Hz, 1H, 1H*), 7.18 (br s, 1H, 1H*), 5.80 (br td, J_{H-F} = 55.8 Hz, *J* = 6.8 Hz, 1H, 1H*), 5.64 (br s, 1H, 1H*), 5.23 (d, *J* = 4.7 Hz, 1H*), 5.15 (d, *J* = 4.7 Hz, 1 H), 4.56 (d, *J* = 6.7 Hz, 1H, 1H*), 4.46 (d, *J* = 12.1 Hz, 1H*), 4.41 (d, *J* = 12.0 Hz, 1 H), 4.30 - 4.22 (m, 1H, 1H*), 4.22 - 4.07 (m, 1H, 1H*), 4.02 - 3.79 (m, 1H, 1H*) 3.92 (br s, 3H, 3H*), 3.73 - 3.52 (m, 2H, 2H*), 3.05 - 2.68 (m, 3H, 3H*), 2.40 - 2.21 (m, 1H, 1H*), 2.13 - 1.94 (m, 4H, 4H*), 1.83 (s, 2H, 2H*), 1.75 - 1.20 (m, 12H, 12H*), 1.12 (s, 9H*),1.1 0 (s, 9H), 1.06 (br d, *J* = 7.3 Hz, 3H, 3H*), 0.92 - 0.85 (m, 4H, 4H*).

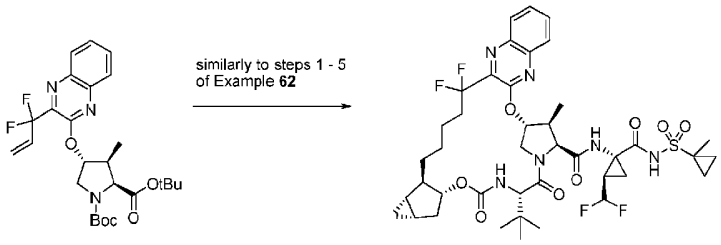
[0298] Example **81.** Preparation of (1aS,2aR,6S,9S,10S,11R,23aR,23bS)-6-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-19,19-difluoro-15-methoxy-10-methyl-4,7-dioxo-1a,2,2a,4,5,6,7,10,11,19,20,21,22,23,23a,23b-hexadecahydro-1 H,9H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19][1,10,3,6]dioxadiazacyclononade cino[11,12-b]quinoxaline-9-carboxamide.



Example 81

[0299] Example **81** was prepared in a similar fashion to Example **62,** substituting Intermediate **A10** for Intermediate **A9** in Step 5. Example **81** was isolated. Analytic HPLC RetTime: 9.36 min. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{42}H_{55}F_4N_6O_9S$: 895.36; found: 895.59. ^{1}H NMR (400 MHz, CD_3OD): δ 9.23 (s, 1 H), 7.93 (d, J = 8.8 Hz, 1 H), 7.31 (dd, J = 8.8, 2.4 Hz, 1 H), 7.26 (d, J = 2.4 Hz, 1 H), 5.80 (td, J_{H-F} = 56 Hz, J = 6.8 Hz, 1 H), 5.73 (d, J = 3.2 Hz, 1 H), 4.94 (d, J = 7.2 Hz, 1 H), 4.56 (d, J = 6.8 Hz, 1 H), 4.36 (d, J = 6.8 Hz, 1 H), 4.32 (s, 1 H), 4.22-4.16 (dd, J = 12, 4 Hz, 1 H), 3.97 (s, 3H), 2.79-2.71 (m, 1 H), 2.61-2.52 (m, 1 H), 2.26-2.16 (m, 1 H), 2.08-1.92 (m, 4H), 1.82-1.64 (m, 3H), 1.60-1.54 (m, 3H), 1.53-1.46 (m, 1 H), 1.52 (s, 3H), 1.44-1.26 (m, 5H), 1.08 (s, 9H), 1.07-0.98 (m, 4H), 0.94-0.84 (m, 3H), 0.60-0.48 (m, 2H).

[0300] Example **82.** Preparation of (1aS,2aR,6S,9S,10S,11R,23aR,23bS)-6-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-19,19-difluoro-10-methyl-4,7-dioxo-1a,2,2a,4,5,6,7,10,11,19,20,21,22,23,23a,23b-hexadecahydro-1H,9H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19][1,10,3,6]dioxadiazacyclononade cino[11,12-b]quinoxaline-9-carboxamide



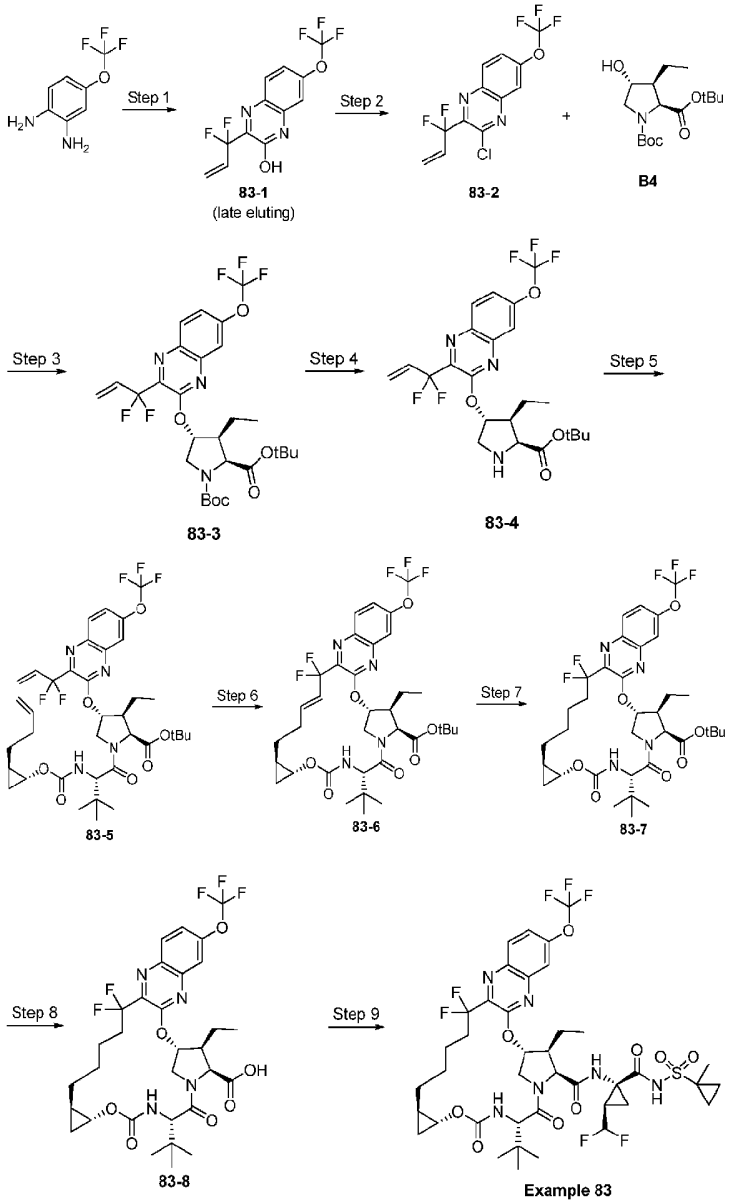
82-1

Example 82

[0301] Intermediate **82-1** was prepared in a similar fashion to intermediate **46-2,** substituting intermediate **E3** with **E4** in Step 1. LCMS-ESI$^+$ (m/z): $[M+H]^+$calcd for $C_{26}H_{34}F_2N_3O_5$: 506.25; found: 506.59.

[0302] Example **82** was prepared in a similar fashion to Example **62,** substituting Intermediate **82-1** for Intermediate **46-2** in Step 1. Example **82** was isolated. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{41}H_{52}F_4N_6O_8S$: 864.35; found: 865.43. ^{1}H NMR (400 MHz, $cdcl_3$) δ 9.82 (s, 1 H), 7.89 - 7.72 (m, 2H), 7.67 (t, *J* = 7.6 Hz, 1 H), 6.93 (s, 1 H), 6.12 - 5.65 (m, 2H), 5.34 (d, *J* = 8.6 Hz, 1 H), 4.90 (d, *J* = 7.4 Hz, 1 H), 4.45 (t, *J* = 9.3 Hz, 2H), 4.27 (d, *J* = 7.9 Hz, 1 H), 4.13 (dd, *J* = 11.9, 3.9 Hz, 1 H), 2.77 - 2.64 (m, 2H), 2.27 - 2.12 (m, 1 H), 2.13 - 1.86 (m, 4H), 1.82 - 1.19 (m, 15H), 1.18 - 0.98 (m, 13H), 0.89 - 0.77 (m, 2H), 0.53 (dd, *J* = 13.3, 8.1 Hz, 1 H), 0.43 (d, *J* = 4.2 Hz, 1 H).

[0303] Example **83.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1 R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-18,18-difluoro-3,6-dioxo-14-(trifluoromethoxy)-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Step 1. Preparation of **83-1:** HATU (3.06 g, 8.05 mmol) was added slowly to a solution of 3,3-difluoro-2-oxopent-4-enoic acid (1.03 g, 6.86 mmol) in 10 mL of DMF. A mixture of 4-(trifluoromethoxy)benzene-1,2-diamine (1.29 g, 6.71 mmol) and DIPEA (1.4 mL, 8.05 mmol) in 12 mL of DMF was then added. After stirring overnight, reaction mixture was poured into 175 mL of water and extracted with ethyl acetate (4 x 100 mL). Combined organics were washed with 50% brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Resulting solid was purified via silica gel column chromatography (0-25% ethyl acetate in hexanes) to yield intermediate **83-1,** the late eluting product. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{12}H_8F_5N_2O_2$: 307.04; found: 307.29.

Step 2. Preparation of **83-2:** A solution of **83-1** (924 mg, 3.01 mmol) in 2 mL DMF was treated with $POCl_3$ (0.56 mL, 6.04 mmol) and heated at 80 °C for 2.5 hours. After cooling to room temperature, reaction mixture was diluted with 25 mL of EtOAc and added slowly to 20 mL of water with vigorous stirring. Layers were separated and aqueous was extracted with ethyl acetate. Combined organics were washed subsequently with saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give intermediate **83-2.** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{12}H_7ClF_5N_2O$: 324.01; found: 324.13.

Step 3. Preparation of **83-3:** Cs_2CO_3 (606 mg, 1.86 mmol) was added to a mixture of intermediate **83-2** (460 mg, 1.54 mmol) and intermediate **B4** (564 mg, 1.79 mmol) in 12 mL of DMF at room temperature. Reaction mixture was heated at 85 °C overnight. After cooling to room temperature, mixture was poured into 50 mL of water and extracted with ethyl acetate (4 x 40 mL). Combined

organics were washed with 90 mL of 50% brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Resulting solid was purified via silica gel column chromatography (0-30% ethyl acetate in hexanes) to give **83-3.** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{28}H_{35}F_5N_3O_6$: 604.24; found: 604.20.

Step 4. Preparation of **83-4:** Quinoxaline ether **83-3** (290 mg, 0.647 mmol) was dissolved in 4.1 mL of tert-butyl acetate and 1.1 mL of dichloromethane at room temperature. $MeSO_3H$ (0.25 mL, 3.88 mmol) was added dropwise and reaction mixture stirred at rt for 2 h. The reaction mixture was transferred to a stirred mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ (30 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford amine **83-4.** LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{27}F_5N_3O_4$: 504.18; found: 504.31.

Step 5. Preparation of **83-5:** HATU (260 mg, 0.684 mmol, Oakwood) and DIPEA (0.40 mL, 2.30 mmol) were added to a mixture of **83-4** (258 mg, 0.512 mmol) and Intermediate **D11** (177 mg, 0.657 mmol) in 7 mL of acetonitrile under argon. After stirring overnight, the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (0-20% ethyl acetate in hexanes) to yield **83-5.** LCMS-ESI$^+$ (m/z): $[M+H]^+$ calcd for $C_{37}H_{48}F_5N_4O_7$: 755.34; found: 755.49.

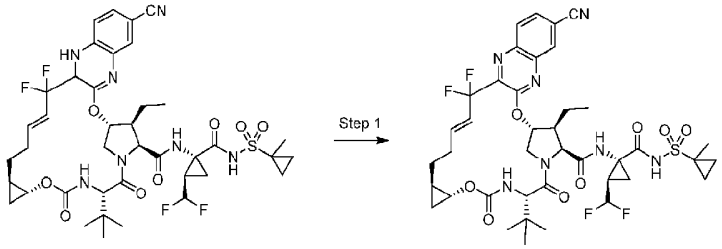
Step 6. Preparation of **83-6:** A mixture of **83-5** (215 mg, 0.285 mmol) and Zhan 1 B catalyst (29 mg, 0.040 mmol, Strem) in 60 mL of DCE was deoxygenated with argon for 15 minutes. The mixture was then heated at reflux for 90 minutes. After cooling to room temperature, reaction mixture was concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-40% ethyl acetate in hexanes) to yield **83-6.** LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{35}H_{44}F_5N_4O_7$: 727.31; found: 727.43.

Step 7. Preparation of **83-7:** Palladium on carbon (10 wt % Pd, 40 mg, 0.038 mmol) was added to a solution of **83-6** (129 mg, 0.178 mmol) in 9 mL of ethanol. The atmosphere was replaced with hydrogen and the reaction stirred overnight. The reaction mixture was filtered over Celite and washed with ethanol. Filtrate was concentrated *in vacuo* to yield a residue, which was purified via silica gel column chromatography (0-30% ethyl acetate in hexanes) to yield **83-7.** LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{35}H_{46}F_5N_4O_7$: 729.32; found: 729.45.

Step 8. Preparation of **83-8:** TFA (0.62 mL, 8.09 mmol) was added slowly to a solution of **83-7** (79 mg, 0.109 mmol) in 1.8 mL of dichloromethane. After 4 hours, mixture was concentrated under reduced pressure to near dryness. Resulting residue was taken up in 10 mL of ethyl acetate, washed with 8 mL of water, 8 mL of sat. $NaHCO_3$ (aq), and separated. Aqueous layers were extracted with ethyl acetate (3 x 10 mL). Combined organics were washed with 10 mL of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield **83-8,** which was used in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{38}F_5N_4O_7$: 673.26; found: 673.10.

Step 9. Preparation of Example **83:** HATU (84 mg, 0.221 mmol, Oakwood) and DIPEA (0.095 mL, 0.547 mmol) were added to a mixture of **83-8** (72 mg, 0.107 mmol) and Intermediate **A10** (66 mg, 0.217 mmol) in 4 mL of acetonitrile under argon. After stirring for overnight, reaction mixture was taken up in 20 mL of ethyl acetate and washed with 10 mL of 1 N aqueous HCl. The aqueous layer was extracted three times with ethyl acetate. Combined organics were washed with 50% brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-50% ethyl acetate in hexanes) and reverse phase prep HPLC (50-100% acetonitrile in water, with 0.1% trifluoroacetic acid buffer) to yield the trifluoroacetic acid salt of Example **83.** Analytic HPLC RetTime: 9.12 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{40}H_{50}F_7N_6O_9S$: 923.32; found: 923.10. ^1H NMR (400 MHz, CD_3OD): δ 9.26 (s, 1H), 8.01-7.91 (m, 2H), 7.78-7.63 (m, 1 H), 5.95 (d, J = 3.6 Hz, 1 H), 5.83 (td, J_{H-F} = 61 Hz, J = 6.0 Hz, 1 H), 4.59 (d, J = 7.2 Hz, 1 H), 4.42 (d, J = 12.4 Hz, 1 H), 4.35 (s, 1 H), 4.22-4.11 (m, 1 H), 3.72-3.66 (m, 1 H), 2.71-2.49 (m, 2H), 2.18-1.94 (m, 3H), 1.90-1.75 (m, 3H), 1.74-1.62 (m, 2H), 1.60-1.48 (m, 3H), 1.51 (s, 3H), 1.50-1.24 (m, 4H), 1.22-1.18 (m, 2H), 1.08 (s, 9H), 1.07-0.84 (m, 5H), 0.81-0.64 (m, 1 H), 0.54-0.44 (m, 1 H).

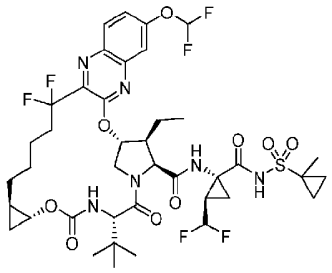
[0304] Example **84.** Preparation of (1aR,5S,8S,9S,10R,19E,22aR)-5-tert-butyl-14-cyano-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-18,18-difluoro-3,6-dioxo-1,1a,3,4,5,6,9,10,18,21,22,22a-dodecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 78 Example 84

Step 1: Preparation of Example **84.** Crude Example **78** (8.7 mg, 0.01 mmol) was redissolved in ACN (0.3 mL) and treated with DDQ (3.4 mg, 0.015 mmol). After 10 min, the solution was directly purified by reverse phase HPLC (Gemini 5u C18 110Å column, 50-100% ACN/H_2O + 0.1% TFA) and lyophilized to afford the TFA salt of Example **84.** Analytical HPLC RetTime: 8.385 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for C40H47F4N7O8S: 861.90; found: 862.89. ^{1}H NMR (400 MHz, CD30D) ^{1}H NMR (400 MHz, CD3OD) δ 9.21 (s, 1 H), 8.25 (d,1 H), 8.20 (d,1 H), .7.91 (dd, 1 H),6.32 (m, 2H), 5.97-5.61 (m, 2H), 4.82 (m, 1 H), 4.58 - 4.13 (m, 4H), 3.71-3.49 (m, 3H), 2.61 (m, 2H), 2.23 (m, 1 H), 2.00 - 1.80 (m, 3H), 1.56 - 1.20 (m, 10H), 1.20 (m, 3H), 1.07 (m, 8H), 0.98-0.82 (m, 3H)., 0.55 (m, 1 H).

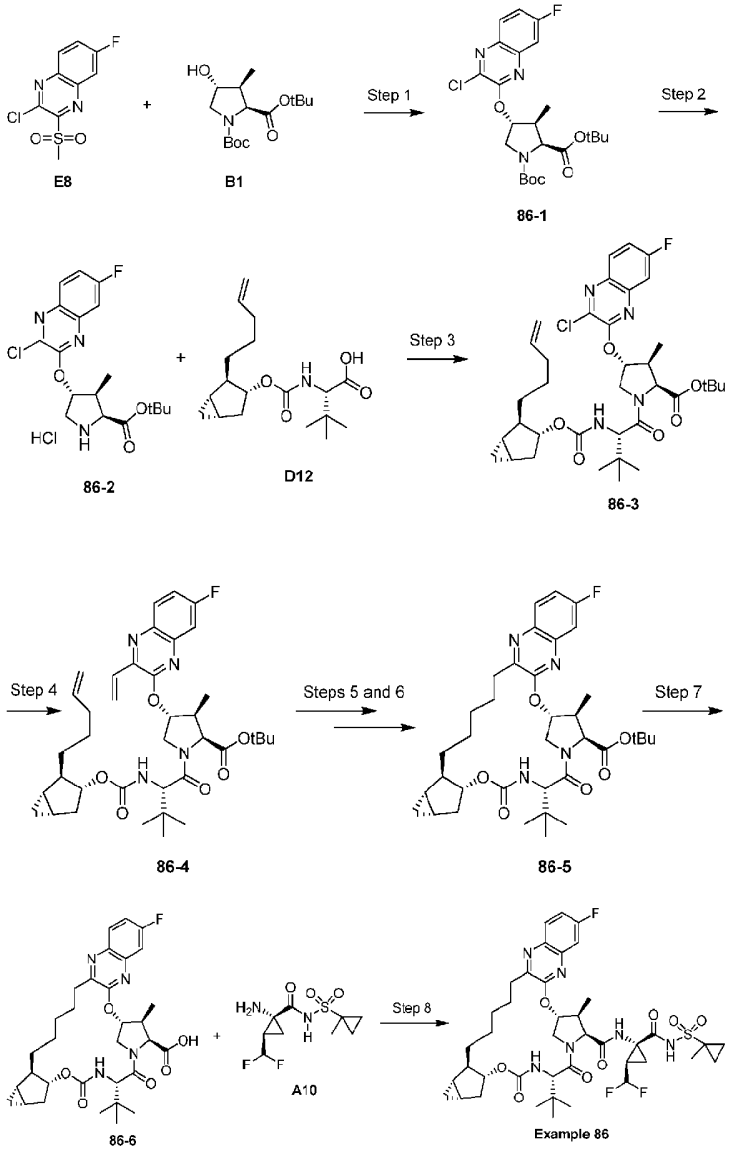
[0305] Example **85.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-14-(difluoromethoxy)-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-18,18-difluoro-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 85

[0306] Example **85** was prepared similarly to Example **83,** by using intermediate **E7** in place of **83-2** in step 3. Analytical HPLC RetTime: 8.725 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for C40H50F6N6O9S: 904.92; found: 905.16. ^{1}H NMR (400 MHz, CD3OD) δ 9.23 (s, 1 H), 7.88 (d,1 H), 7.76 (d,1 H), .7.62 (dd, 1 H), 7.03 (dd, 1 H), 5.94-5.65 (m, 3H), 4.57 - 4.14 (m, 4H), 3.66 (m, 1 H), 2.57 (m, 2H), 2.01 - 1.97 (m, 3H), 1.82 - 1.77 (m, 3H), 1.64 (m, 1 H), 1.57 - 1.33 (m, 10H), 1.20 (m, 3H), 1.06-0.87 (m, 12H), 0.87 (m, 2H)., 0.48 (m, 1 H).

[0307] Example **86.** Preparation of (1aS,2aR,6S,9S,10S,11R,23aR,23bS)-6-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-15-fluoro-10-methyl-4,7-dioxo-1a,2,2a,4,5,6,7,10,11,19,20,21,22,23,23a,23b-hexadecahydro-1H,9H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19][1,10,3,6]dioxadiazacyclononade cino[11,12-b]quinoxaline-9-carboxamide.



Step 1. Preparation of **86-1:** To a solution of **E8** (1.5 g, 5.75 mmol) and **B1** (1.9 g, 6.34 mmol) in MeCN (50 mL) is added Cs_2CO_3 (3.09 g, 9.49 mmol). After stirring at rt for 60 h, the reaction mixture was filtered over celite and concentrated. The crude residue was purified by silica gel chromatography (5-35% EtOAc/hexanes) to yield product **86-1.** LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{23}H_{30}ClFN_3O_5$ - Boc: 482.13; found: 382.04.

Step 2. Preparation of **86-2:** To a solution of **86-1** (747 mg, 1.55 mmol) in CH_2Cl_2 (5 mL) is added HCl (5 mL, 4 M in dioxane) and allowed to stir for 3 h. The reaction mixture was concentrated to give a residue that was used subsequently without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{23}C_{12}FN_3O_3$ - HCl: 382.13; found: 382.08.

Step 3. Preparation of **86-3:** To a solution of **86-2** (397 mg, 0.95 mmol), **D12** (308 mg, 0.95 mmol) and BEP (312 mg, 1.14 mmol) in EtOAc (9 mL) and NMP (1 mL) was added DIPEA (0.7 mL, 3.8 mmol) and the reaction was stirred at 50 °C overnight. The reaction was quenched with sat. $NaHCO_3$ solution and extracted with EtOAc, washed subsequently with brine, dried over magnesium sulfate and concentrated. The crude product was purified by silica gel to yield **86-3.** LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{36}H_{49}ClFN_4O_6$: 687.33; found: 687.44.

Step 4. Preparation of **86-4:** To a solution of **86-3** (266 mg, 0.39 mmol), TEA (0.08 mL, 0.58 mmol) and potassium vinyltrifluoroborate (78 mg, 0.58 mmol) in EtOH (8 mL) was added $PdCl_2$(dppf) (32 mg, 0.04 mmol). The reaction was degassed with N_2 for 10 min and heated to 75 °C for 1 h. The reaction was quenched with sat. $NaHCO_3$ solution and extracted with EtOAc, washed subsequently with brine, dried over magnesium sulfate and concentrated. The residue was purified using silica gel

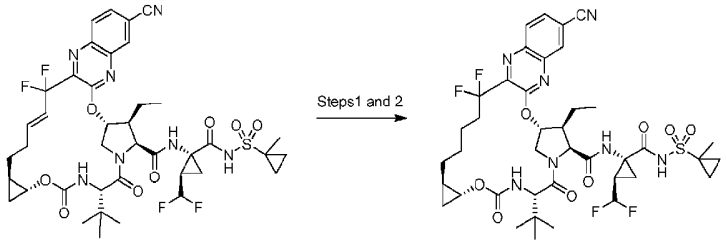
chromatography (0-25% EtOAc/hexanes) to give **86-4.** LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{38}H_{52}FN_4O_6$: 679.39; found: 679.52.

Step 5 and 6. Preparation of **86-5:** To a solution of **86-4** (262 mg, 0.38 mmol) in DCE (50 mL) was added Zhan 1 B catalyst (28 mg, 0.04 mmol) and the reaction was degassed for 25 minutes with N_2. The reaction was heated to 100 °C for 1 h, allowed to cool to rt and concentrated. The crude product was purified by silica gel chromatography (0-30% EtOAc/hexanes) to give olefin product (182 mg; LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{36}H_{48}FN_4O_6$: 651.36; found: 651.38) that was taken up in EtOH (5 mL) and EtOAc (1 mL) and treated with Pd/C (10%, 55 mg). The atmosphere was replaced with hydrogen and stirred at rt for 1.25 h. The reaction was filtered over Celite, washed with EtOAc and concentrated to give **86-5** that was used subsequently without further purification. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{36}H_{50}FN_4O_6$: 653.37; found: 653.46.

Step 7. Preparation of **86-6:** To a solution of **86-5** (182 mg, 0.28 mmol) in DCM (3 mL) was added TFA (3 mL) and stirred at rt for 18 h. The reaction was diluted with EtOAc, washed with H_2O, basicified to pH 7 with sat. $NaHCO_3$ solution, washed with 1 M citric acid solution, dried over magnesium sulfate, and concentrated to give a residue of **86-6** that was used subsequently without further purification. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{32}H_{42}FN_4O_6$: 597.31; found: 597.15.

Step 8. Preparation of Example **86:** To a solution of **86-6** (24 mg, 0.04 mmol), intermediate **A10** (18 mg, 0.06 mmol), TBTU (23 mg, 0.07 mmol) and DMAP (7 mg, 0.06 mmol) in DMF (3 mL) was added DIPEA (35 µL, 0.20 mmol) and the reaction was stirred at rt for 3 h. Additional intermediate **A10** (18 mg, 0.06 mmol), TBTU (23 mg, 0.07 mmol), DMAP (7 mg, 0.06 mmol), and DIPEA (35 µL, 0.20 mmol) was added and the reaction was stirred at rt for 16 h. The crude material was purified by reverse phase HPLC (Gemini, 30-85% ACN/H_2O + 0.1% TFA) and lyophilized to give Example **86** as a TFA salt. Analytical HPLC RetTime: 9.25 min.LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{41}H_{54}F_3N_6O_8S$: 847.37; found: 847.18. ^{1}HNMR (400 MHz, CD_3OD) δ 9.18 (s, 1H), 8.13 - 7.84 (m, 2H), 7.59 - 7.21 (m, 2H), 6.07 - 5.58 (m, 2H), 5.00 (d, *J* = 7.4 Hz, 1 H), 4.57 (d, *J* = 7.0 Hz, 1 H), 4.45 - 4.27 (m, 2H), 4.20 (dd, J = 12.0, 4.0 Hz, 1 H), 3.11 - 2.94 (m, 3H), 2.92 - 2.70 (m, 4H), 2.32 - 2.14 (m, 1 H), 2.10 - 1.94 (m, 2H), 1.86 (m, 1 H), 1.77 (d, *J* = 14.5 Hz, 1 H), 1.74 - 1.21 (m, 15H), 1.21 - 1.01 (m, 10H), 1.00 - 0.84 (m, 2H), 0.60 (m, 1H), 0.53 (m, 1 H).

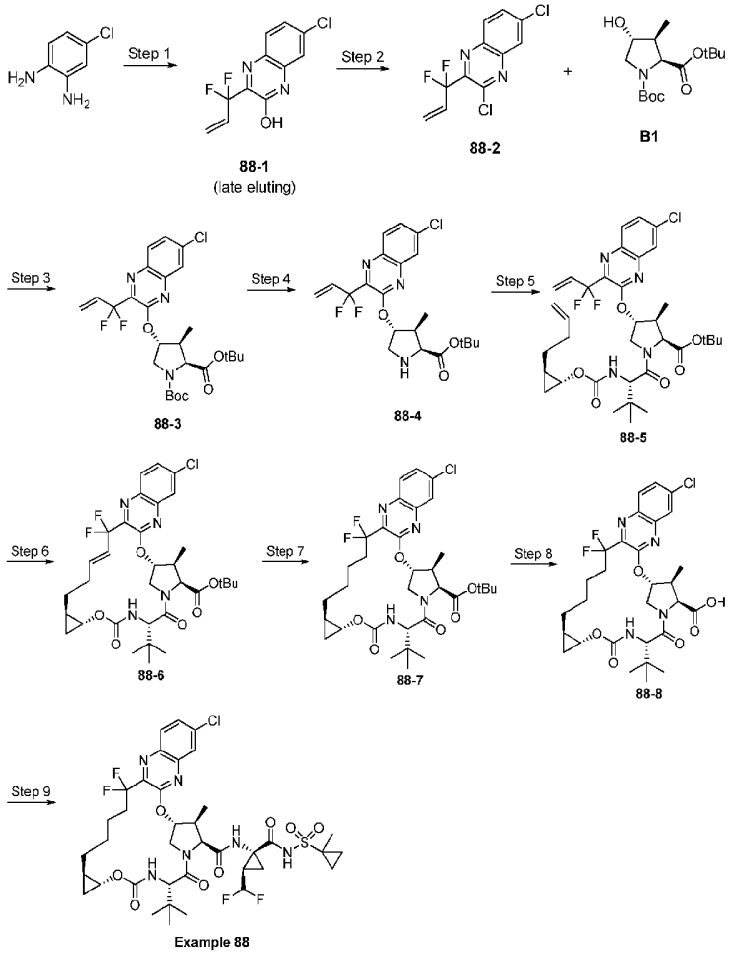
[0308] Example **87.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-14-cyano-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-18,18-difluoro-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 84 Example 87

[0309] Steps 1 and 2. Preparation of Example **87.** To a solution of Example **84** (100 mg, 0.11 mmol) in EtOAc (3 mL) was added Pd/C (10 wt % Pd, 30 mg). The reaction vessel was purged twice with H_2 and was stirred at rt under 1 atm H_2 for 6h. After which time the reaction mixture was filtered through a pad of celite and concentrated. The reaction reduced the quinoxaline ring. The crude material was redissolved in ACN (5 mL) and treated with DDQ (34 mg, 0.15 mmol). After 1 h, the solution was directly purified by reverse phase HPLC (Gemini 5u C18 110A column, 50-100% ACN/H_2O + 0.1% TFA) and lyophilized to afford the TFA salt of Example **87.** Analytical HPLC RetTime: 8.463 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for C40H49F4N7O8S: 863.92; found: 864.18. ^{1}HNMR (400 MHz, CD3OD) δ 9.24 (s, 1 H), 8.27 (d,1 H), 8.20 (d,1 H), .7.91 (dd, 1 H), 5.93-5.82 (m, 3H), 4.88 (m, 1 H), 4.58 - 4.13 (m, 5H), 3.71-3.49 (m, 3H), 2.59 (m, 2H), 2.03 - 1.96 (m, 3H), 1.82 - 1.77 (m, 3H), 1.65 - 1.35 (m, 11 H), 1.20 (m, 3H), 1.06-0.87 (m, 8H), 0.71 (m, 2H)., 0.48 (m, 1 H).

[0310] Example **88.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-14-chloro-N-[(1 R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-18,18-difluoro-9-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide



Step 1. Preparation of **88-1:** HATU (4.56 g, 12 mmol) was added slowly to a solution of 3,3-difluoro-2-oxopent-4-enoic acid (1.52 g, 10.1 mmol) in 14 mL of DMF. A mixture of 4-chlorobenzene-1,2-diamine (1.43 g, 10 mmol) and DIPEA (2.1 mL, 12 mmol) in 20 mL of DMF was then added. After stirring overnight, reaction mixture was poured into 30 mL of 1 N aqueous HCl and extracted with ethyl acetate (5 x 40 mL). Combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Resulting solid was purified via silica gel column chromatography (0-45% ethyl acetate in hexanes) to yield intermediate **88-1** as the late eluting product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.1 (s, 1 H), 7.99 (m, 1 H), 7.61-7.58 (m, 1 H), 7.33-7.31 (m, 1 H), 6.61-6.48 (m, 1 H), 5.96 -5.90 (m, 1 H), 5.67-5.63 (m, 1 H).

Step 2. Preparation of **88-2:** A solution of intermediate **88-1** (648 mg, 2.53 mmol) in 2 mL DMF was treated with $POCl_3$ (0.49 mL, 5.26 mmol) and heated at 80 °C for 3 hours. After cooling to room temperature, reaction mixture was diluted with 20 mL of EtOAc and added slowly to 15 mL of water with vigorous stirring. Layers were separated and aqueous was extracted with ethyl acetate. Combined organics were washed subsequently with saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give intermediate **88-2.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.184 (d, J = 1.6Hz, 1 H), 8.01 (d, J = 8.8 Hz, 1 H), 7.82 (dd, J = 9.4, 2 Hz, 1 H), 6.56-6.43 (m, 1 H), 5.88 (m, 1 H), 5.70 (d, J = 10.8 Hz, 1 H).

Step 3. Preparation of **88-3:** Cs_2CO_3 (660 mg, 2.03 mmol) was added to a mixture of intermediate **88-2** (425 mg, 1.54 mmol) and intermediate **B1** (570 mg, 1.89 mmol) in 9 mL of DMF at room temperature. Reaction mixture was heated at 85 °C overnight. After cooling to room temperature, mixture was poured into 40 mL of water and extracted with ethyl acetate (4 x 30 mL). Combined organics were washed with 75 mL of 50% brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Resulting solid was purified via silica gel column chromatography (0-20% ethyl acetate in hexanes) to give **88-3.** LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{26}H_{33}ClF_2N_3O_5$: 540.20; found: 540.12.

Step 4. Preparation of **88-4:** Quinoxaline ether **88-3** (458 mg, 0.848 mmol) was dissolved in 4.2 mL of tert-butyl acetate and 1.2 mL of dichloromethane at room temperature. $MeSO_3H$ (0.30 mL, 4.67 mmol) was added dropwise and reaction mixture stirred at rt for 2 h. The reaction mixture was transferred to a stirred mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ (30 mL). The

phases were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford amine **88-4** as a yellow solid film LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{21}H_{25}ClF_2N_3O_3$: 440.15; found: 440.29.

Step 5. Preparation of **88-5:** HATU (360 mg, 0.947 mmol, Oakwood) and DIPEA (0.51 mL, 2.91 mmol) were added to a mixture of **88-4** (320 mg, 0.727 mmol) and Intermediate **D11** (237 mg, 0.880 mmol) in 10 mL of acetonitrile under argon. After stirring overnight, the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (0-20% ethyl acetate in hexanes) to yield **88-5.** LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{35}H_{46}ClF_2N_4O_6$: 691.30; found: 691.50.

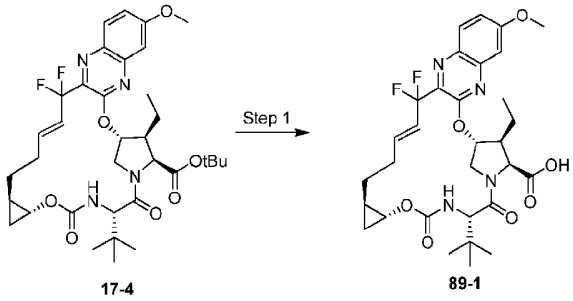
Step 6. Preparation of **88-6:** A mixture of **88-5** (390 mg, 0.564 mmol) and Zhan 1B catalyst (55 mg, 0.075 mmol, Strem) in 100 mL of DCE was deoxygenated with argon for 15 minutes. The mixture was then heated at reflux for 110 minutes. After cooling to room temperature, reaction mixture was concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-25% ethyl acetate in hexanes) to yield **88-6.** LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{33}H_{42}ClF_2N_4O_6$: 663.27; found: 663.33.

Step 7. Preparation of mixture of **88-7:** Rhodium on alumina (5 wt % Rh, 31 mg, 0.015 mmol) was added to a solution of **88-6** (90 mg, 0.136 mmol) in 9 mL of ethanol. The atmosphere was replaced with hydrogen and mixture was stirred overnight. The reaction was filtered over Celite, washing with ethanol. LC/MS analysis indicated about 60% starting material remained. A solution of the residue in 8 mL of ethanol was resubjected to hydrogenation conditions utilizing 25 mg of Rhodium on alumina (5 wt % Rh) overnight. The reaction was filtered over Celite, washing with ethanol. Filtrate was concentrated *in vacuo* to yield as residue, which was purified via silica gel column chromatography (0-30% ethyl acetate in hexanes) to yield **88-7.** LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{44}ClF_2N_4O_6$: 665.28; found: 665.48.

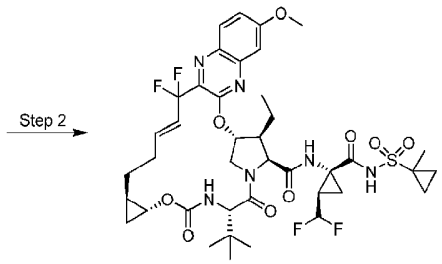
Step 8. Preparation of **88-8:** TFA (0.45 mL, 5.86 mmol) was added slowly to a solution of **88-7** (52 mg, 0.078 mmol) in 2 mL of dichloromethane. After 3 hours, mixture was concentrated under reduced pressure to near dryness. Resulting residue was taken up in 10 mL of ethyl acetate, washed with 8 mL of water, 8 mL of sat. $NaHCO_3$ (aq), and separated. Aqueous layers were extracted with ethyl acetate (3 x 10 mL). Combined organics were washed with 10 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to yield 88-8, which was used in the next step without further purification. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{29}H_{36}ClF_2N_4O_6$: 609.22; found: 609.42.

Step 9. Preparation of Example **88:** HATU (58 mg, 0.153 mmol, Oakwood) and DIPEA (0.065 mL, 0.374 mmol) were added to a mixture of **88-8** (45 mg, 0.074 mmol) and Intermediate **A10** (49 mg, 0.161 mmol) in 2.5 mL of acetonitrile under argon. After stirring for overnight, reaction mixture was taken up in 15 mL of ethyl acetate and washed with 10 mL of 1 N aqueous HCl. The aqueous layer was extracted three times with ethyl acetate. Combined organics were washed with 50% brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-50% ethyl acetate in hexanes) and reverse phase prep HPLC (50-100% acetonitrile in water, with 0.1% trifluoroacetic acid buffer) to yield the trifluoroacetic acid salt of Example **88.** Analytic HPLC RetTime: 8.92 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{38}H_{48}ClF_4N_6O_8S$: 859.28; found: 859.42. ^{1}HNMR (400 MHz, CD_3OD): δ 9.23 (s, 1 H), 8.10 (s, 1 H), 7.90 (d, J = 8.8 Hz, 1 H), 7.81 (d, J = 8.8 Hz, 1 H), 5.81 (td, J_{H-F} = 56 Hz, J = 6.0 Hz, 1 H), 5.69-5.66 (m, 1 H), 4.56 (d, J = 7.2 Hz, 1 H), 4.43 (d, J = 12 Hz, 1 H), 4.34 (s, 1 H), 4.22-4.16 (dd, J = 12, 4 Hz, 1 H), 3.71-3.66 (m, 1 H), 2.83-2.76 (m, 1 H), 2.61-2.48 (m, 1 H), 2.11-1.94 (m, 4H), 1.88-1.72 (m, 4H), 1.71-1.62 (m, 1 H), 1.58-1.54 (m, 2H), 1.51 (s, 3H), 1.50-1.36 (m, 2H), 1.09 (s, 9H), 1.08-1.01 (m, 3H), 1.01-0.94 (m, 2H), 0.93-0.86 (m, 2H), 0.80-0.68 (m, 1 H), 0.52-0.46 (m, 1 H).

[0311] Example **89.** Preparation of (1aR,5S,8S,9S,10R,19E,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-18,18-difluoro-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,21,22,22a-dodecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



17-4 89-1

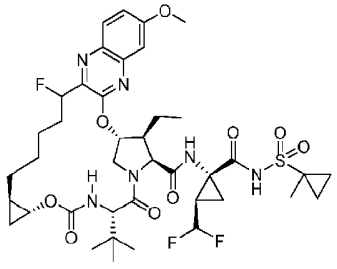


Example 89

Step 1. Preparation of **89-1: 17-4** (95 mg, 0.14 mmol) in 0.4 mL DCM was treated with 0.4 mL TFA and stirred at rt for 2 h. The reaction mixture was diluted with 5 mL DCM and then treated with water and saturated sodium bicarbonate to pH 6.5. The layers were separated and the organic phase was washed once more with water, then dried over anhydrous sodium sulfate, filtered and concentrated to give **89-1.** LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{31}H_{39}F_2N_4O_7$: 617.3; found: 616.7.

Step 2. Preparation of Example **89:** A mixture of **89-1** from step 1 (41 mg, 0.066 mmol), Intermediate **A10** (24 mg, 0.079 mmol), HATU (30 mg, 0.079 mmol), and DIPEA (0.057 mL, 0.33 mmol) in DMF (0.4 mL) was stirred at rt overnight. The mixture was diluted with 2 N HCl (1 mL) and extracted with dichloromethane. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product mixture was purified by reverse phase prep HPLC (10-99% acetonitrile in water, with 0.1% trifluoroacetic acid buffer) to give Example **89.** Analytic HPLC RetTime: 8.65 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{40}H_{51}F_4N_6O_9S$: 867.3; found: 866.9. ^{1}HNMR (400 MHz, $CDCl_3$) δ 9.890 (s, 1 H), 7.98 (d, *J* = 9.2 Hz, 1 H), 7.28 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.06 (d, *J* = 2.8 Hz, 1 H), 6.75 (br s, 1 H), 6.30 - 5.93 (m, 2H), 5.92 (td, J_{H-F} = 52 Hz, *J* = 6.8 Hz, 1 H), 5.47 (d, *J* = 10 Hz, 1H), 4.53 (d, *J* = 12 Hz, 1 H), 4.48 (d, *J* = 10.4 Hz, 1H), 4.42 (d, *J* = 6.8 Hz, 1 H), 4.07 (dd, *J* = 11.6, 3.2 Hz, 1 H), 3.98 - 3.94 (m, 1 H), 3.95 (s, 3H), 3.57 (m, 1 H), 2.60 - 2.48 (m, 2H), 2.20 (m, 1 H), 2.06 (m, 1 H), 1.90 (m, 1 H), 1.80 (m, 1 H), 1.63 (m, 2H), 1.50 (s, 3H), 1.56 - 1.36 (m, 2H), 1.26 (m, 1 H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.09 (s, 9H), 1.03-0.93 (m, 2H), 0.85 (m, 2H), 0.76 (m, 1 H), 0.53 (m, 1 H).

[0312] Example **90.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-9-ethyl-18-fluoro-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.

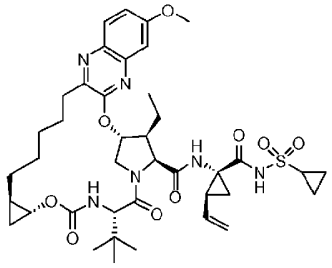


Example 90

[0313] Further purification of a synthesis of compound **17** by reverse phase prep HPLC (60-88% acetonitrile in water, with 0.1% trifluoroacetic acid buffer) allowed isolation of example **93** as a minor side product. Analytic HPLC RetTime: 8.64 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{40}H_{54}F_3N_6O_9S$: 851.4; found: 851.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (br s, 1 H), 7.88 (d, *J* = 9.1 Hz, 1

H), 7.22 (d, *J* = 2.4 Hz, 1 H), 7.06 (d, *J* = 2.4 Hz, 1 H), 6.55 (s, 1 H), 5.91 (td, J_{H-F} = 136 Hz, *J* = 8 Hz, 1 H), 5.81 (td, J_{H-F} = 52 Hz, *J* = 8 Hz, 1 H), 5.30 (d, *J* = 9.7 Hz, 1 H), 4.44 (d, *J* = 12.0 Hz, 1 H), 4.38 (d, *J* = 6.7 Hz, 1 H), 4.32 (d, *J* = 9.8 Hz, 1 H), 4.07 (m, 1 H), 3.93 (s, 3H), 3.72 (m, 1 H), 2.59 (m, 1 H), 2.35 (m, 1 H), 2.06 (m, 4H), 1.88 (m, 1 H), 1.78 (m, 1 H), 1.71 - 1.52 (m, 4H), 1.48 (s, 3H), 1.48 - 1.41 (m, 2H), 1.23 (m, 2H) 1.21 (t, *J* = 8.0 Hz, 3H), 1.08 (s, 9H), 1.05 - 0.90 (m, 2H), 0.84 (m, 2H), 0.66 (m, 1 H), 0.48 (m, 1 H).

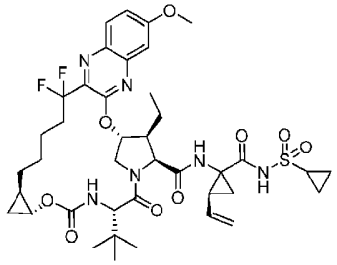
[0314] Example **91.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-{(1R,2S)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyll-9-ethyl-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 91

[0315] Example **91** was prepared similarly to Example **1** substituting Intermediate **A1** for Intermediate **A10** in Step 8. The TFA salt of Example **91** was isolated. Analytic HPLC RetTime: 8.72 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{40}H_{55}N_6O_9S$: 795.96; found: 795.94. ^{1}H NMR (400 MHz, CD3OD) δ 9.03 (s, 1 H); 7.80 (d, J =9.2 Hz, 1 H); 7.24 (dd, J = 9.2, 2.4 Hz, 1 H); 7.16 (d, J = 2.4 Hz, 1 H); 5.90 (d, J = 3.6 Hz, 1 H); 5.68 (m, 1 H); 5.25 (d, J = 17.2 Hz, 1.6 Hz, 1 H); 5.10 (d, J = 11.2, 1.6 Hz, 1 H); 4.57 (d, J = 6.8 Hz, 1 H); 4.39 (br s, 1 H); 4.37 (d, J = 9.2 Hz, 1 H); 4.16 (dd, J =12.8, 4.4 Hz, 1 H); 3.93 (s, 3H); 3.77-3.72 (m, 1 H); 3.02-2.88 (m, 1 H): 2.86-2.75 (m, 1 H); 2.64-2.54 (m, 1 H); 2.18 (q, J = 8.8 Hz, 1 H): 1.90-1.66 (m, 4H); 1.66-1.40 (m, 6H); 1.38-1.32 (m, 1 H); 1.30-1.20 (m, 5H); 1.10 (s, 9H); 1.14-1.02 (m, 2H); 0.77-0.68 (m, 1 H); 0.54-0.45 (m, 1H).

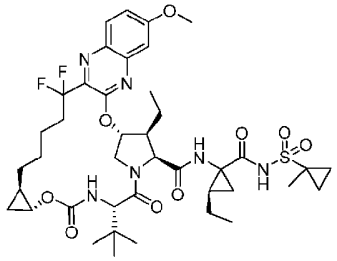
[0316] Example **92.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-{(1R,2S)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-9-ethyl-18,18-difluoro-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro -8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 92

[0317] Example **92** was prepared in a similar fashion to Example **17,** substituting Intermediate **A1** for Intermediate **A10** in Step 7. Example **92** was isolated Analytic HPLC RetTime: 8.75 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{40}H_{53}F_2N_6O_9S$: 831.36; found: 831.25, ^{1}H NMR (400 MHz, Chloroform-d) δ 9.98 (s, 1 H), 7.96 (d, *J* = 9.2 Hz, 1 H), 7.40 - 7.19 (m, 1 H), 7.08 (s, 1 H), 6.56 (s, 1 H), 5.91 (d, *J* = 3.8 Hz, 1 H), 5.86 - 5.64 (m, 1 H), 5.34 (d, *J* = 9.7 Hz, 1 H), 5.21 (d, *J* = 17.2 Hz, 1 H), 5.10 (d, *J* = 10.3 Hz, 1H),4.53-4.26(m,2H),4.15-4.02(m, 1 H), 3.95 (s, 3H), 3.73 - 3.57 (m, 1 H), 2.97 - 2.81 (m, 1 H), 2.64 - 2.37 (m, 2H), 2.21 - 2.06 (m, 1 H), 2.06 - 1.88 (m, 2H), 1.88 - 1.55 (m, 4H), 1.55 - 1.12 (m, 10H), 1.07 (s, 9H), 1.02 - 0.78 (m, 5H), 0.78 - 0.61 (m, 1 H), 0.47 (q, *J* = 7.3, 6.2 Hz, 1 H).

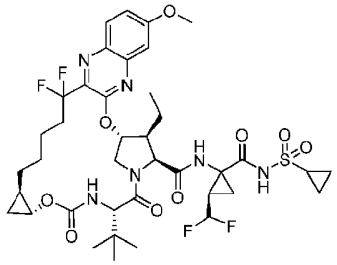
[0318] Example 93. Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-9-ethyl-N-[(2R)-2-ethyl-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-18,18-difluoro-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradeca hydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 93

[0319] Example **93** was prepared in a similar fashion to Example **17,** substituting Intermediate **A4** for Intermediate **A10** in Step 7. Example **93** was isolated Analytic HPLC RetTime: 8.03 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{41}H_{57}F_2N_6O_9S$: 847.39; found: 846.99. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.9 Hz, 1 H), 7.27 (m, 1 H), 7.08 (s, 1 H), 6.65 (s, 1 H), 5.91 (s, 1 H), 5.41 (d, *J* = 9.0 Hz, 1 H), 4.82 (m, 2H), 4.47 (d, *J* = 6.2 Hz, 1 H), 4.35 (dd, *J* = 35.7, 10.7 Hz, 2H), 4.07 (m, 1 H), 3.94 (s, 3H), 3.63 (m, 1 H), 2.50 (m, 2H), 1.95 (m, 2H), 1.94 (m, 2H), 1.78 (m, 3H), 1.64 (m, 4H), 1.48 (m, 6H), 1.19 (m, 4H), 1.07 (s, 9H), 1.05 - 0.88 (m, 4H), 0.88 - 0.75 (m, 1 H), 0.67 (m, 1 H), 0.47 (m, 1 H).

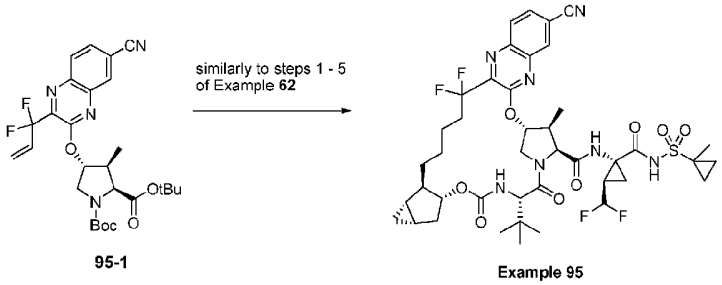
[0320] Example **94.** Preparation of (1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-[(2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-(difluoromethyl)cyclopropyl]-9-ethyl-18,18-difluoro-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradec ahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.



Example 94

[0321] Example **94** was prepared in a similar fashion to Example **17,** substituting Intermediate **A9** for Intermediate **A10** in Step 7. Example **94** was isolated Analytic HPLC RetTime: 8.71 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{39}H_{51}F_4N_6O_9S$: 855.34; found: 855.26. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1 H), 8.02 (d, *J* = 9.2 Hz, 1 H), 7.33 (d, *J* = 12 Hz, 1 H), 7.12 (s, 1 H), 5.95 (td, J_{HF} = 52 Hz, *J* = 8 Hz, 1 H), 5.50 (d, *J* = 9.7 Hz, 1 H), 4.53 (d, *J* = 6.4 Hz, 1 H), 4.46 (dd, *J* = 26.4, 10.7 Hz, 2H), 4.13 (d, *J* = 11.5 Hz, 1 H), 4.00 (s, 3H), 3.68 (m, 1 H), 2.91 (m, 1 H), 2.57 (m, 3H), 2.13 (m, 2H), 1.94 (m, 2H), 1.73 (m, 3H), 1.50 (m, 3H), 1.33 (m, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.13 (s, 9H), 1.00 - 0.95 (m, 4H), 0.95 - 0.85 (m, 1 H), 0.69 (m, 1 H), 0.51 (m, 1 H).

[0322] Example **95.** Preparation of (1aS,2aR,6S,9S,10S,11R,23aR,23bS)-6-tert-butyl-15-cyano-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-19,19-difluoro-10-methyl-4,7-dioxo-1a,2,2a,4,5,6,7,10,11,19,20,21,22,23,23a,23b-hexadecahydro-1H,9H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19][1,10,3,6]dioxadiazacyclononade cino[11,12-b]quinoxaline-9-carboxamide.



95-1

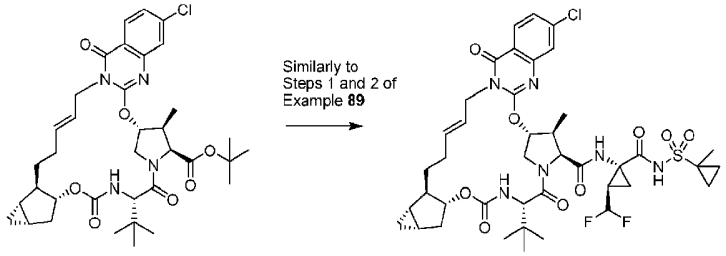
Example 95

[0323] Intermediate **95-1** was prepared in a similar fashion to Intermediate **46-2,** substituting **E6** for Intermediate **E3** in Step 1.

LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{27}H_{33}F_2N_4O_5$: 531.24; found: 531.2.

[0324] Example **95** was prepared in a similar fashion to Example **62,** substituting Intermediate **95-1** for Intermediate **46-2** in Step 1 and substituting Intermediate **A10** for Intermediate **A9** in Step 5. Example **95** was isolated Analytic HPLC RetTime: 8.86 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{42}H_{52}F_4N_7O_8S$: 890.35; found: 889.94. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1 H), 7.80 (m, 2H), 7.42 (d, *J* = 8.6 Hz, 1 H), 6.85 (s, 1 H), 6.69 (s, 1 H), 5.38 (m, 1 H), 5.29 (m, 3H), 5.02 (d, *J* = 8.8 Hz, 1 H), 4.46 (d, *J* = 7.4 Hz, 1 H), 4.10 - 3.97 (m, 2H), 3.84 (d, *J* = 7.9 Hz, 1 H), 3.74 (d, *J* = 8.6 Hz, 1 H), 2.42 - 2.29 (m, 1 H), 2.10 (s, 1 H), 1.87 - 1.72 (m, 1 H), 1.69 - 1.48 (m, 4H), 1.38 (d, *J* = 14.8 Hz, 2H), 1.30 - 1.08 (m, 4H), 0.99 (s, 5H), 0.89 (m, 3H), 0.69 (s, 10H), 0.64 (m, 1 H), 0.43 (s, 1 H), 0.11 (m, 1 H), 0.01 (m, 1 H).

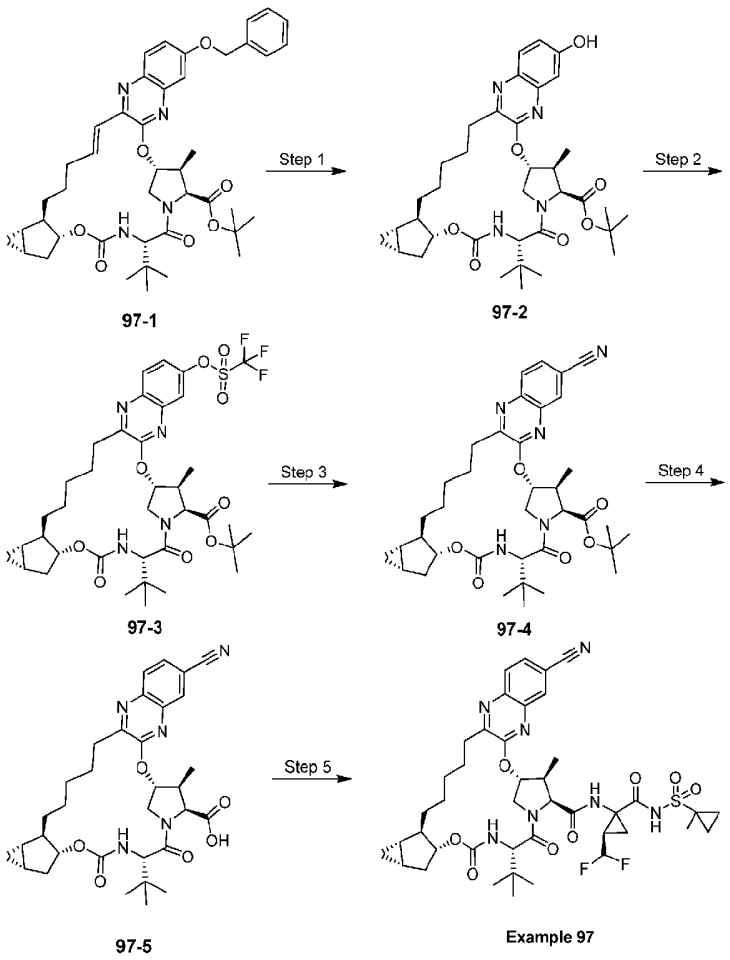
[0325] Example **96.** Preparation of (1aS,2aR,6S,9S,10S,11R,21E,24aR,24bS)-6-tert-butyl-15-chloro-N-[(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-10-methyl-4,7,18-trioxo-1a,2,2a,4,5,6,7,10,11,20,23,24,24a,24b-tetradecahydro-1H,9H,18H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19][1,10,3,6,12]dioxatriazacyclonona decino[11,12-b]quinazoline-9-carboxamide.



96-1 **Example 96**

[0326] Example **96** was prepared in a similar fashion to Example **89,** substituting intermediate **96-1** for intermediate **17-4** in Step 1. Intermediate **96-1** was prepared in a similar fashion to intermediate **17-4** of Example **17,** substituting **E9** for E3 and **B1** for B4 in Step 1, and substituting intermediate **D16** for intermediate **D11** in Step 3. Example **96** was isolated. Analytic HPLC RetTime: 9.18 min. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{41}H_{52}ClF_2N_6O_9S$: 877.32; found: 877.61. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.76 (s, 1 H), 8.03 (d, *J* = 8.6 Hz, 1 H), 7.39 (m, 1 H), 7.27 (m, 1 H), 6.80 (s, 1 H), 5.92 (m, 1 H), 5.87 - 5.73 (m, 1 H), 5.68 (m, 1 H), 5.64 - 5.51 (m, 1 H), 5.21 (m, 1 H), 4.93 (m, 2H), 4.52 - 4.32 (m, 3H), 4.15 - 3.94 (m, 2H), 2.86 - 2.71 (m, 1H), 2.26 (m, 1 H), 2.15 (m, 2H), 2.10 - 2.02 (m, 1 H), 2.02 - 1.84 (m, 2H), 1.77 (m, 2H), 1.61 (s, 3H), 1.50 (m, 4H), 1.42 - 1.17 (m, 6H), 1.17 - 0.92 (m, 10H), 0.92 - 0.78 (m, 2H), 0.51 - 0.37 (m, 1H).

[0327] Example **97.** Preparation of (1aS,2aR,6S,9S,10S,11R,23aR,23bS)-6-tert-butyl-15-cyano-N-[(2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-10-methyl-4,7-dioxo-1 a,2,2a,4,5,6,7,10,11,19,20,21,22,23,23a,23b-hexadecahydro-1H,9H-8,11-methanocyclopropa[4',5']cyclopenta[1',2':18,19][1,10,3,6]dioxadiazacyclononade cino[11,12-b]quinoxaline-9-carboxamide.



[0328] Intermediate **97-1** was prepared in a similar fashion to intermediate **79-5,** substituting **E2** for **E5** in Step 1. LCMS-ESI$^+$ (*m/z*): [M+H]$^+$calcd for $C_{43}H_{55}N_4O_7$: 739.41; found: 739.31.

Step 1. Preparation of **97-2.** Macrocyclic olefin **97-1** (0.84 g, 1.14 mmol) was dissolved in 114 mL ethanol and 114 mL ethyl acetate. After degassing with Argon, 0.84 g of 5% Pd/C Degussa-type was added and the mixture was hydrogenated for 4 hours at 1 atm. Filtration through celite, concentration, and silica gel chromatography (40% - 60% ethyl acetate in hexanes gradient) provided intermediate **97-2.** LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{36}H_{51}N_4O_7$: 651.38; found: 651.32.

Step 2. Preparation of **97-3.** An ice cold solution of macrocycle phenol **97-2** (0.47 g, 0.73 mmol) and triethylamine (0.81 ml, 5.81 mmol) in 3 mL DCM was treated with trifluoromethanesulfonic anhydride solution, 1 M in methylene chloride (0.18 ml, 1.09 mmol) dropwise. After stirring for 2 hours, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated. Silica gel chromatography using a 5% - 50% ethyl acetate in hexanes gradient gave **97-3** as the first eluting peak (55 mg). LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{37}H_{50}F_3N_4O_9S$: 783.33; found: 782.96.

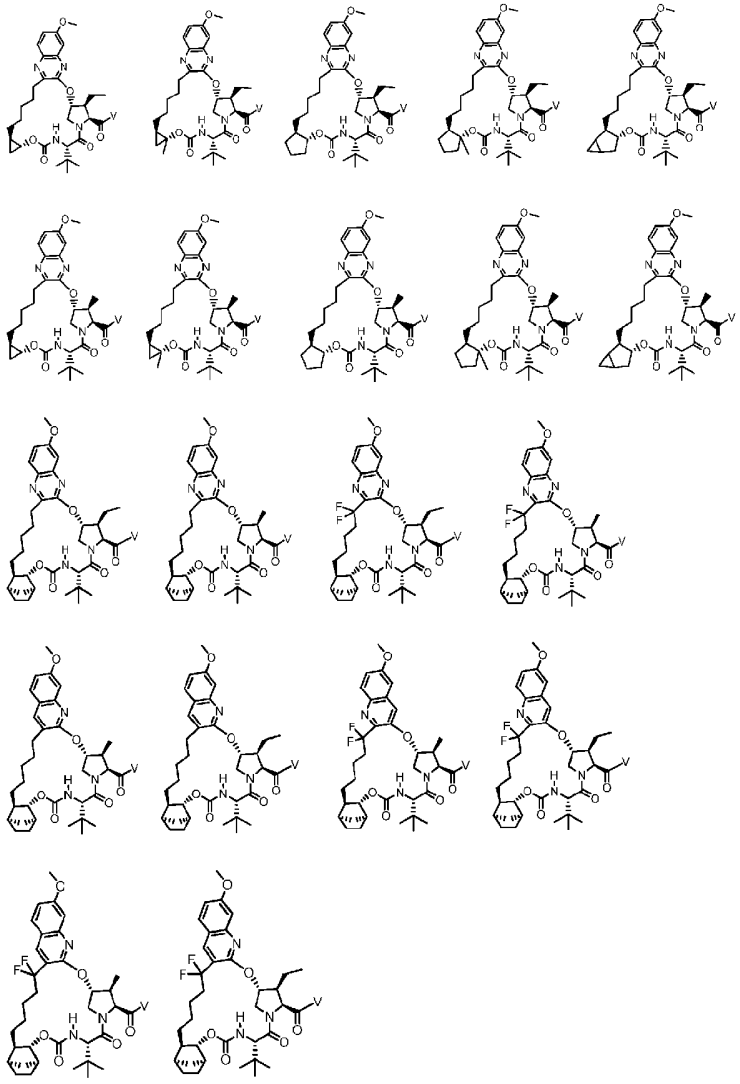
Step 3. Preparation of **97-4.** Degassed a mixture of macrocycle triflate **97-3** (408 mg, 0.52 mmol), tetrakis(triphenylphosphine)palladium (30.11 mg, 0.03 mmol), Zinc cyanide, 98% (61.21 mg, 0.52 mmol) in 2.6 mL DMF for 10 minutes. The reaction was heated at 80 °C for 1 hour. An additional 60 mg tetrakis(triphenylphosphine)palladium and 120 mg Zinc cyanide were added and heating was continued for 30 minutes. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over anhydrous sodium sulphate, filtered and concentrated. The crude product was purified by silica gel chromatography using a gradient of 5% -70% ethyl acetate in hexanes to give intermediate **97-4 .** LCMS-ESI$^+$ (*m/z*): [M+H]$^+$ calcd for $C_{37}H_{50}N_5O_6$: 660.38; found: 660.10.

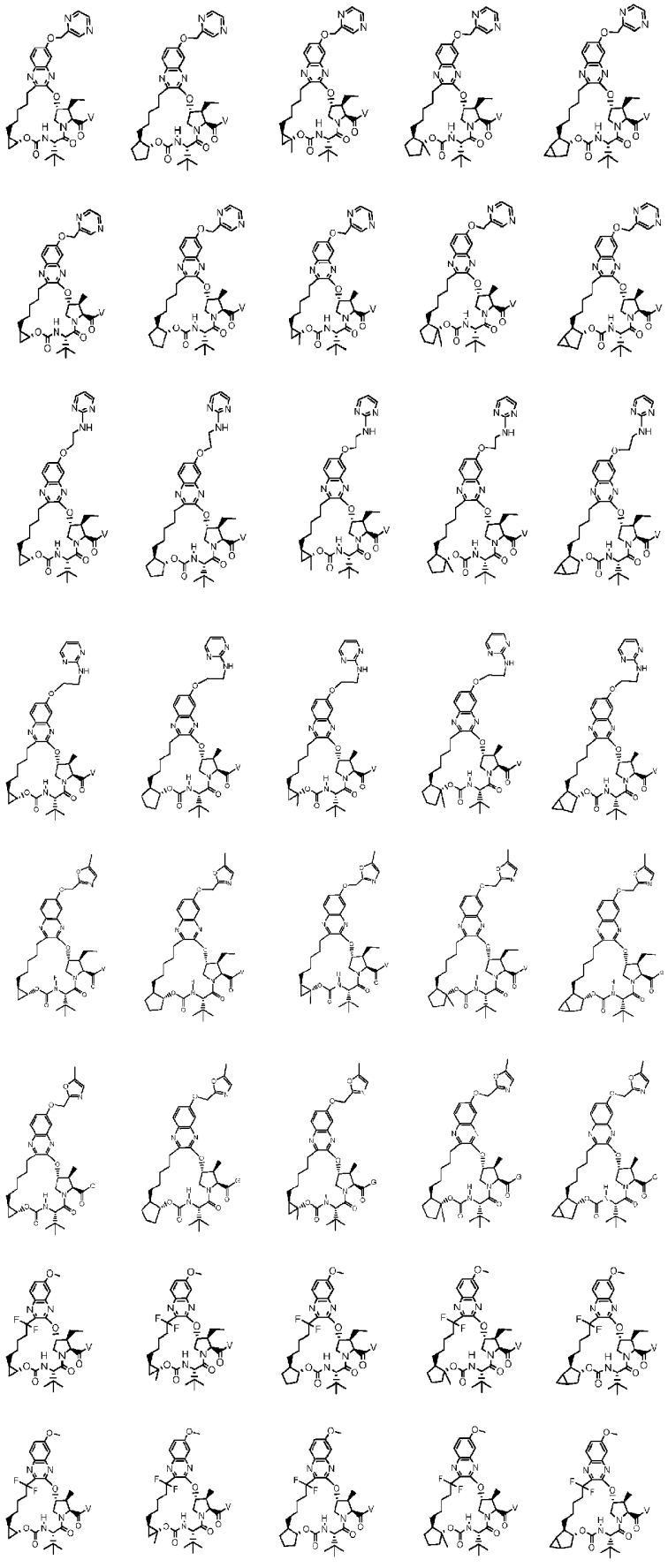
Step 4. Preparation of **97-5.** A solution of **97-4** (290 mg, 0.44 mmol) in 1 mL DCM was treated with 0.5 mL of TFA and stirred

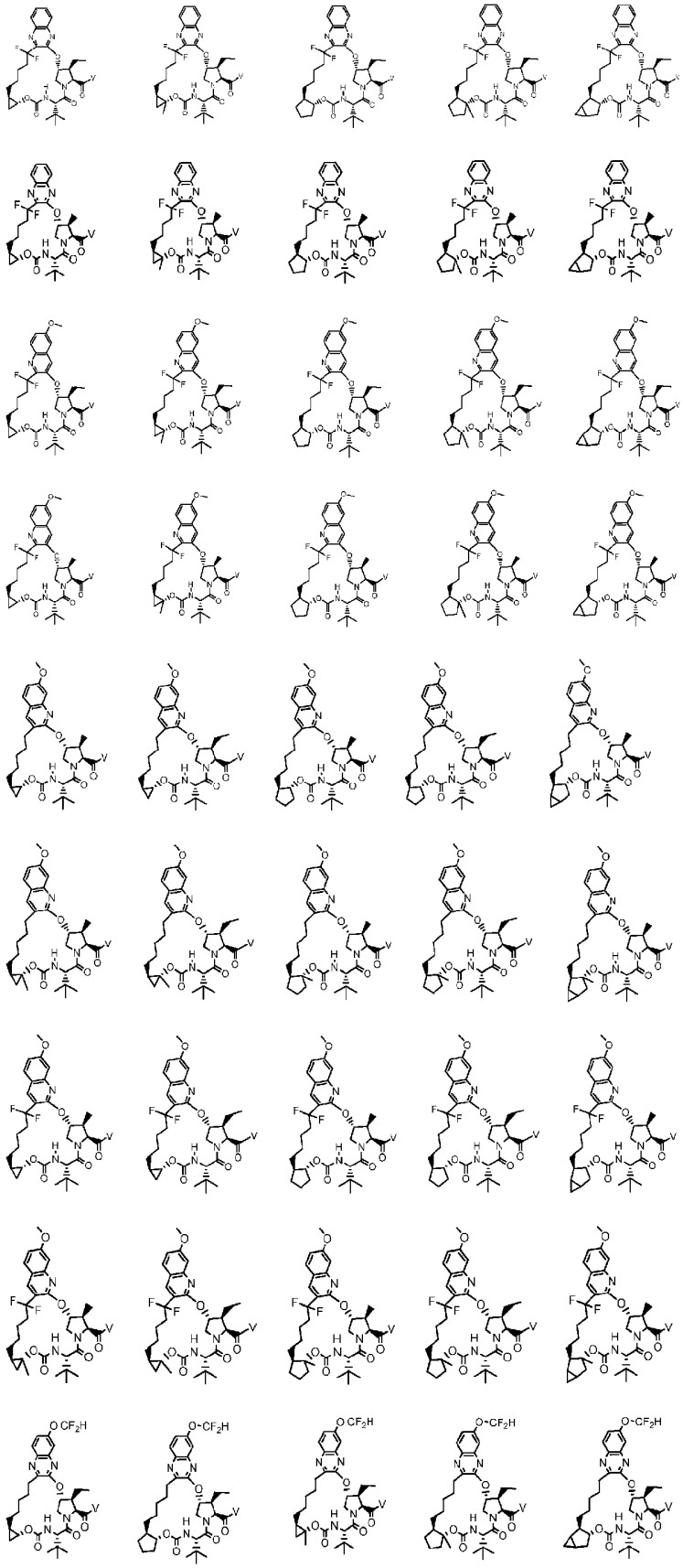
overnight. Water was added and the mixture was extracted with ethyl acetate. The organic phase was separated, dried over anhydrous sodium sulphate, filtered and concentrated. The crude product was purified by silica gel chromatography using a gradient of 10% -70% ethyl acetate in hexanes to give intermediate **97-5** (216 mg) as a white solid. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{33}H_{42}N_5O_6$: 604.31; found: 604.00.

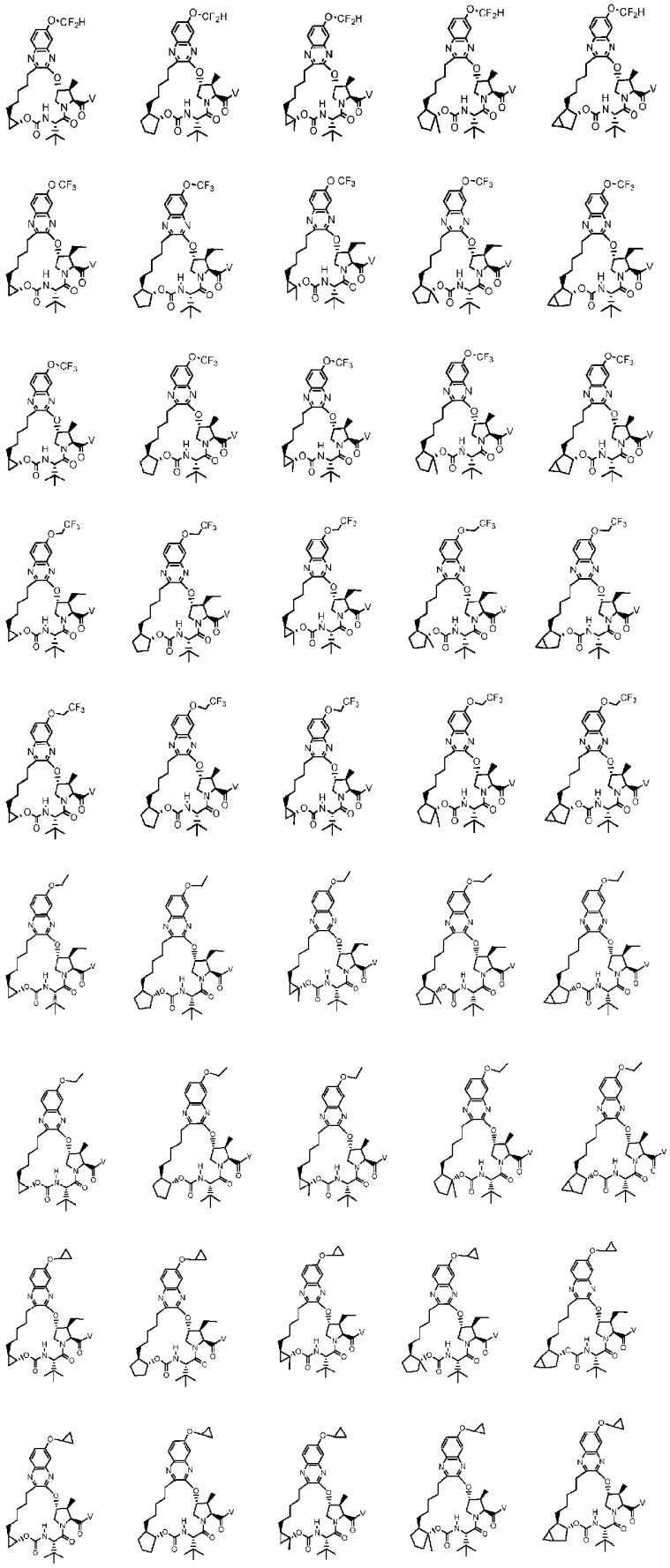
Step 5. Preparation of Example **97.** A mixture of **97-5** (50 mg, 0.08 mmol), HATU (37.79 mg, 0.1 mmol), in 0.3 mL DMF was stirred 5 min, then **A10** (50 mg, 0.08 mmol) and DIPEA (0.06 ml, 0.33 mmol) were added. After 45 min at rt, the reaction was incomplete (LCMS). Added another 20 mg of **A10** and stirred for 2 hours. 2 mL of 1 N HCl was added, and the mixture was extracted with DCM. The crude product was purified by silica gel chromatography using a gradient of 30% - 65% ethyl acetate in hexanes. Combined product fractions contained some residual DMF. Water was added, which generated a precipitate (14 mg). The filtrate was extracted with ethyl acetate, and the extracts were combined with the precipitate. The resulting solution was dried over anhydrous sodium sulphate, filtered, concentrated and dried under reduced pressure to give Example **97.** Analytic HPLC RetTime: 9.06 min. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$calcd for $C_{42}H_{54}F_2N_7O_8S$: 854.98; found: 853.88. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (br s, 1 H), 8.05 (m, 1 H), 7.93 (m, 1 H), 7.62 (m, 1 H), 7.20 (m, 1 H), 7.08 (m, 1 H), 6 - 5.65 (m, 1 H), 5.56 (m, 1 H), 5.17 (m, 1 H), 4.90 (m, 1 H), 4.38 (m, 2H), 4.22 (m, 1 H), 4.06 (m, 1 H), 3.57 (m, 1 H), 2.88 (m, 1 H), 2.70 (m, 5H), 2.28 - 2.08 (m, 1 H), 2.04 - 1.30 (m, 12H), 1.29 - 1.09 (m, 9H), 1.08 - 0.96 (m, 4H), 0.85 - 0.67 (m, 3H), 0.43 (m, 1 H), 0.34 (m, 1 H), 0.19 - 0.03 (m, 1 H).

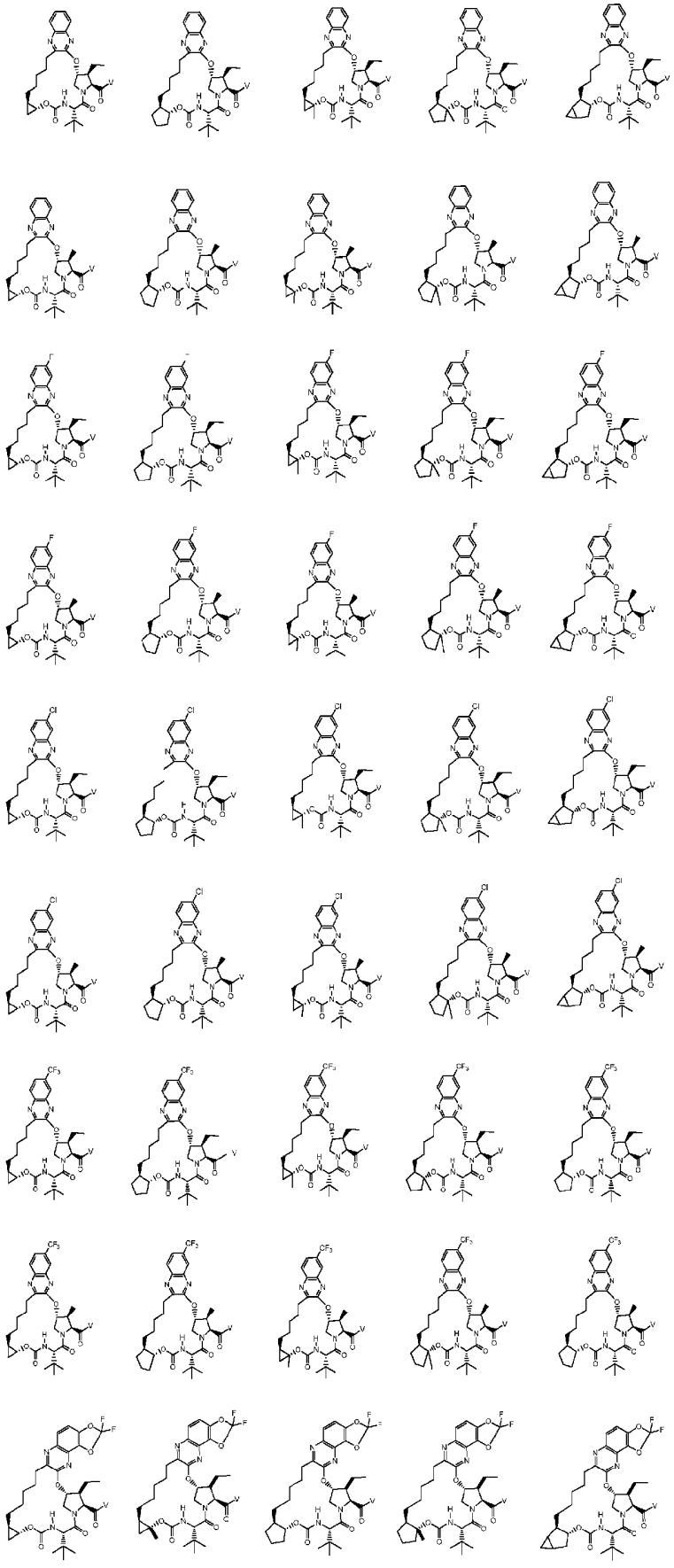
[0329] The following compounds can be made with the synthetic methods of this disclosure, or by means generally well known in the art:

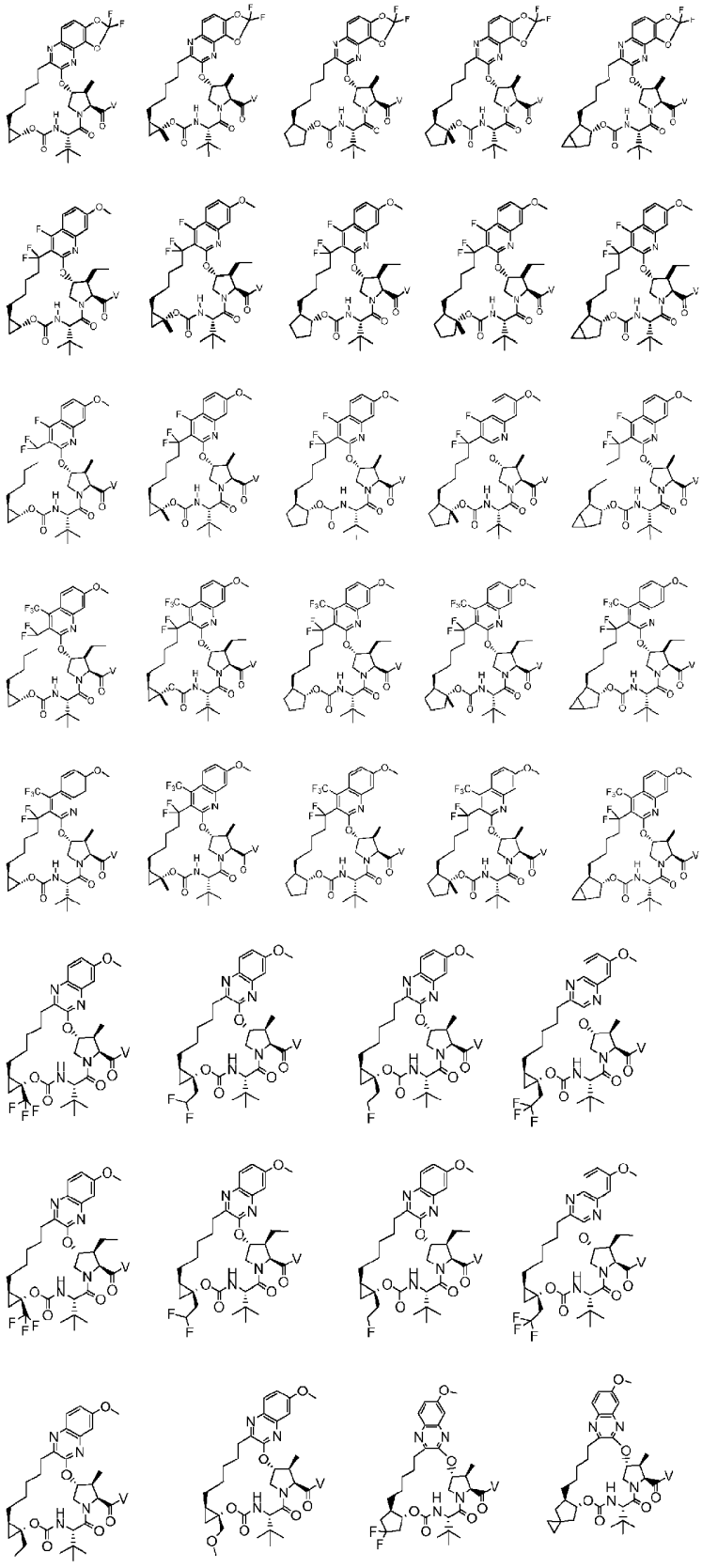


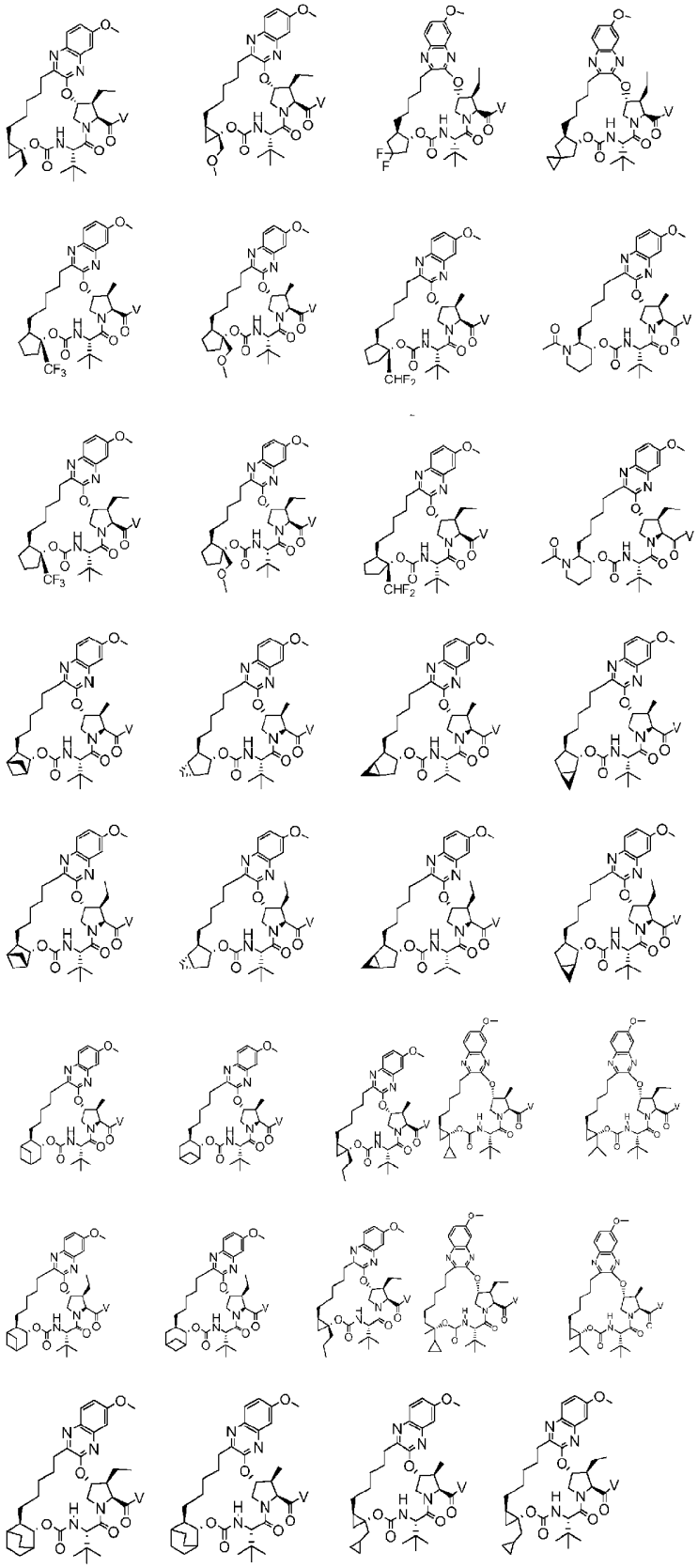


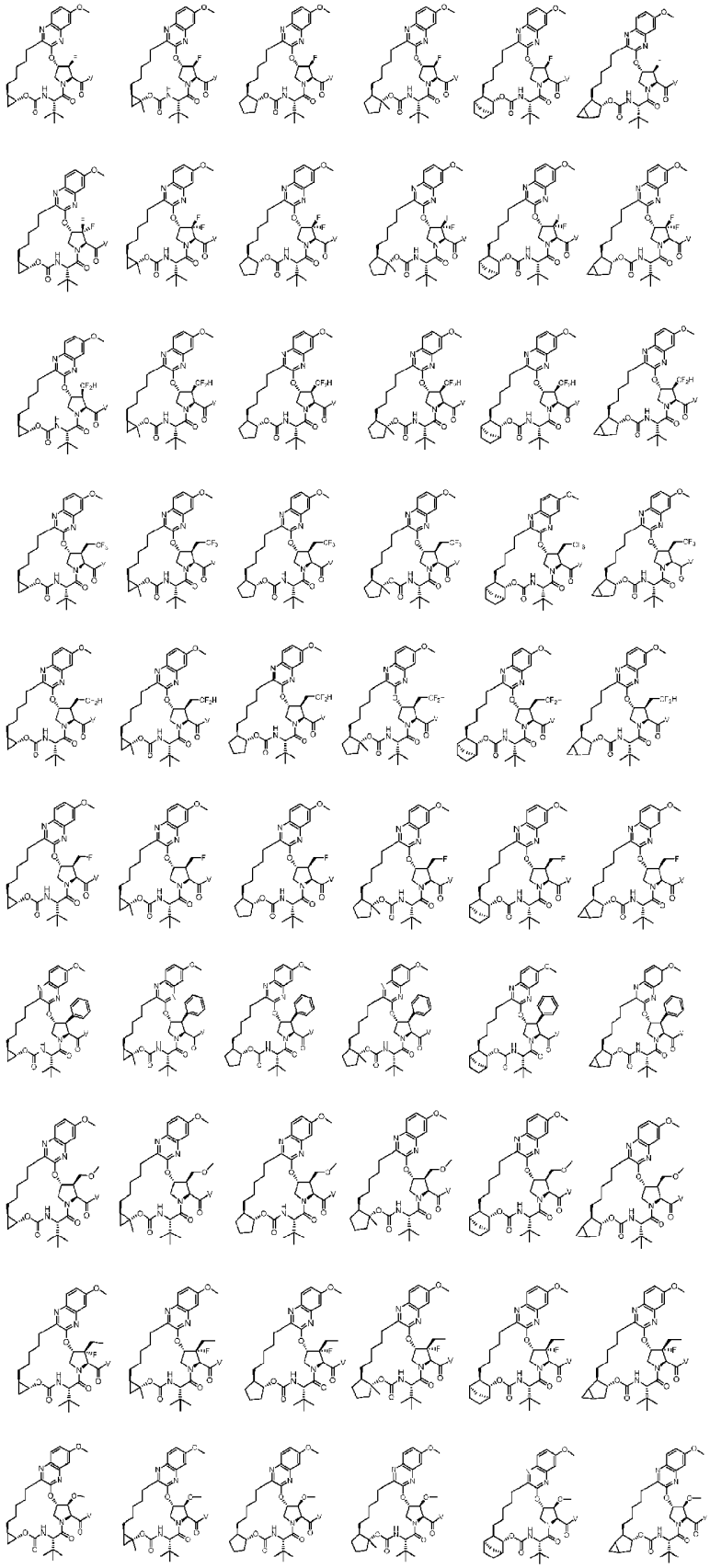


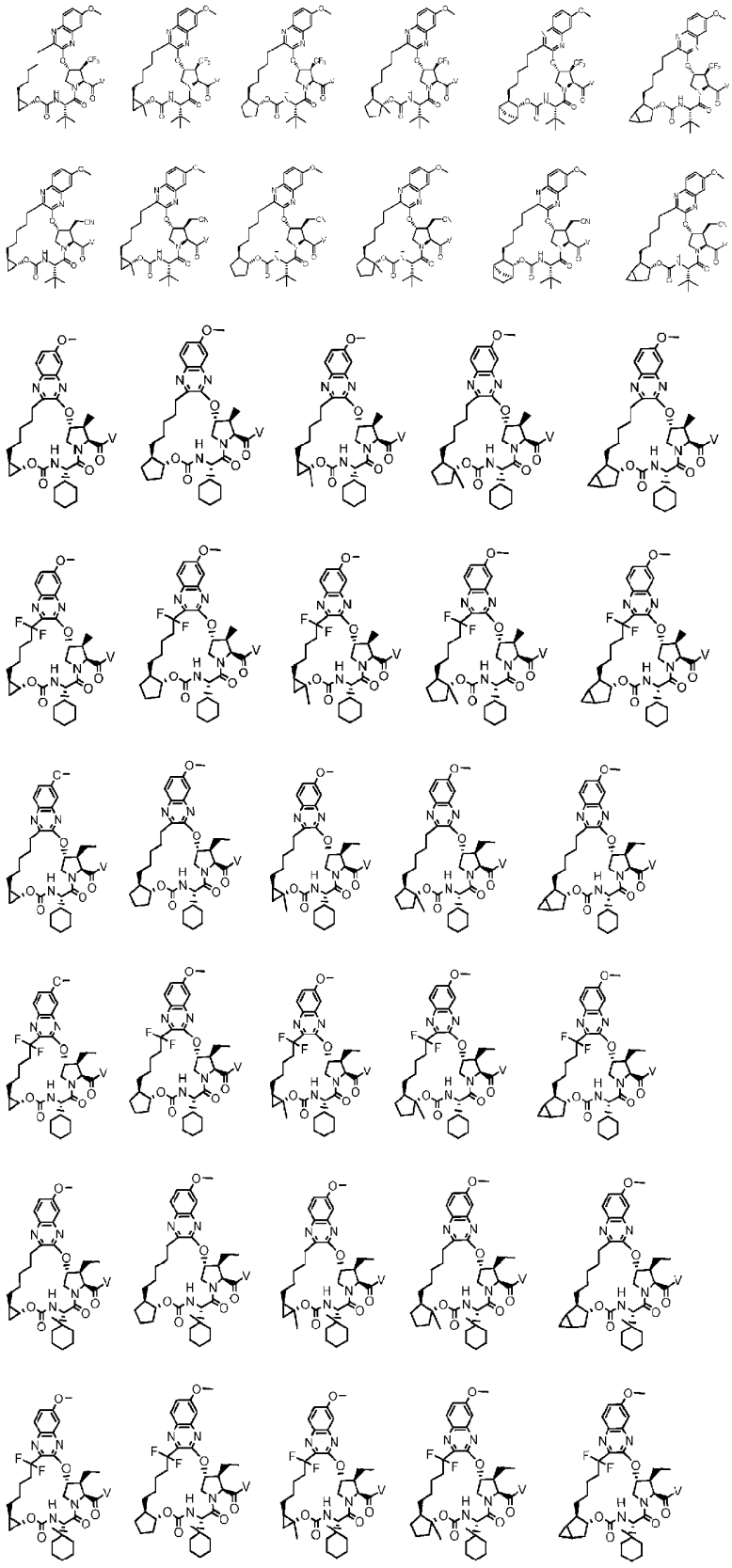


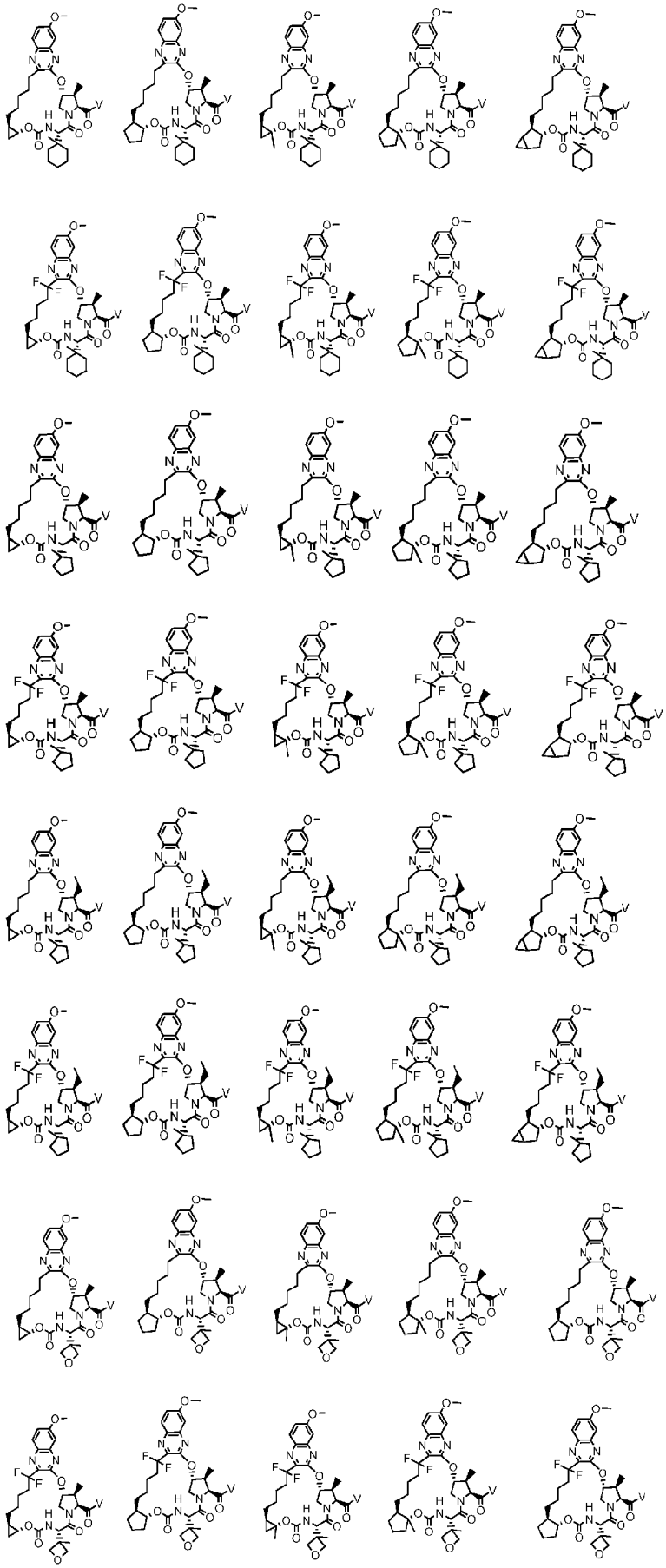


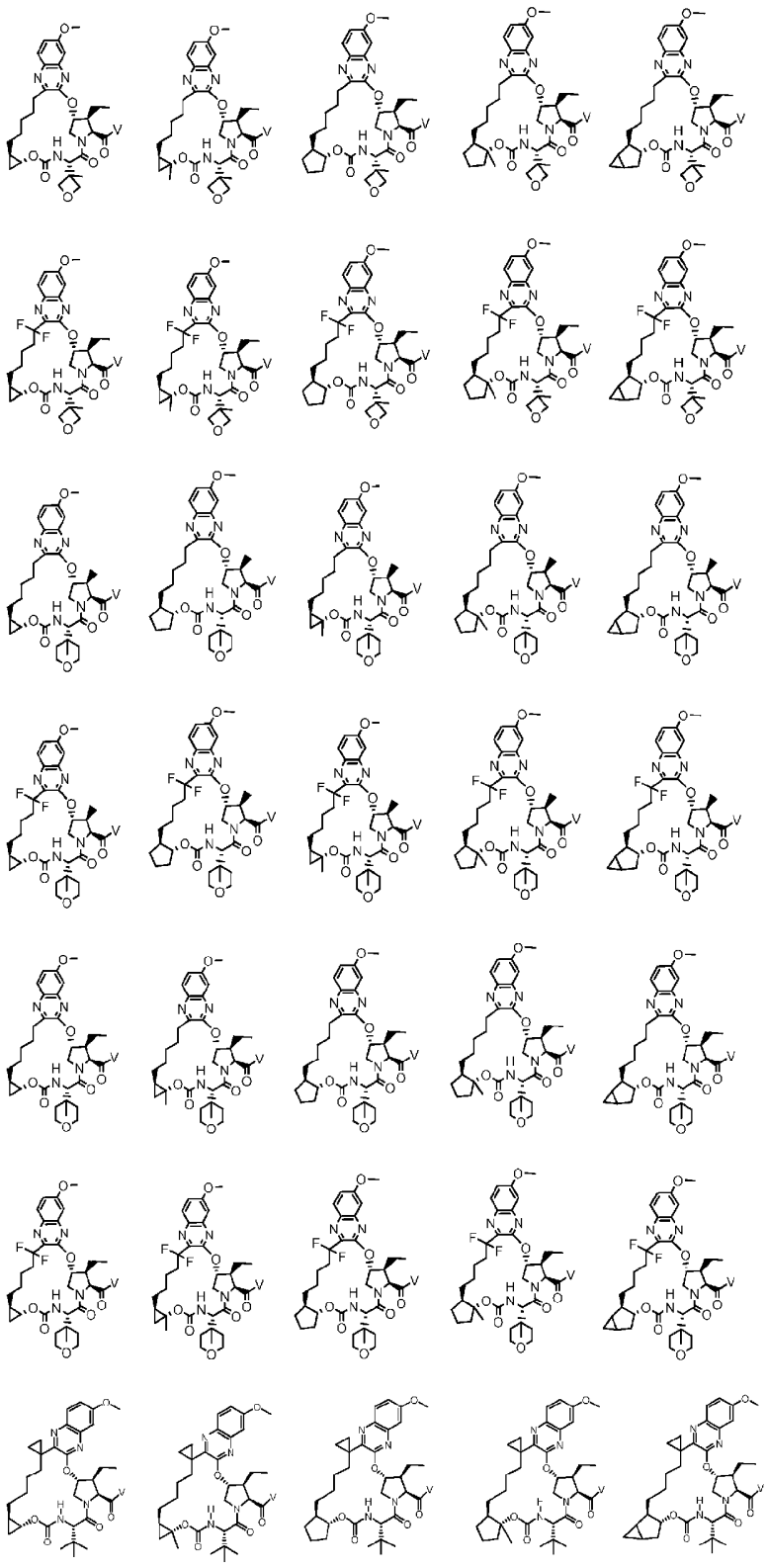


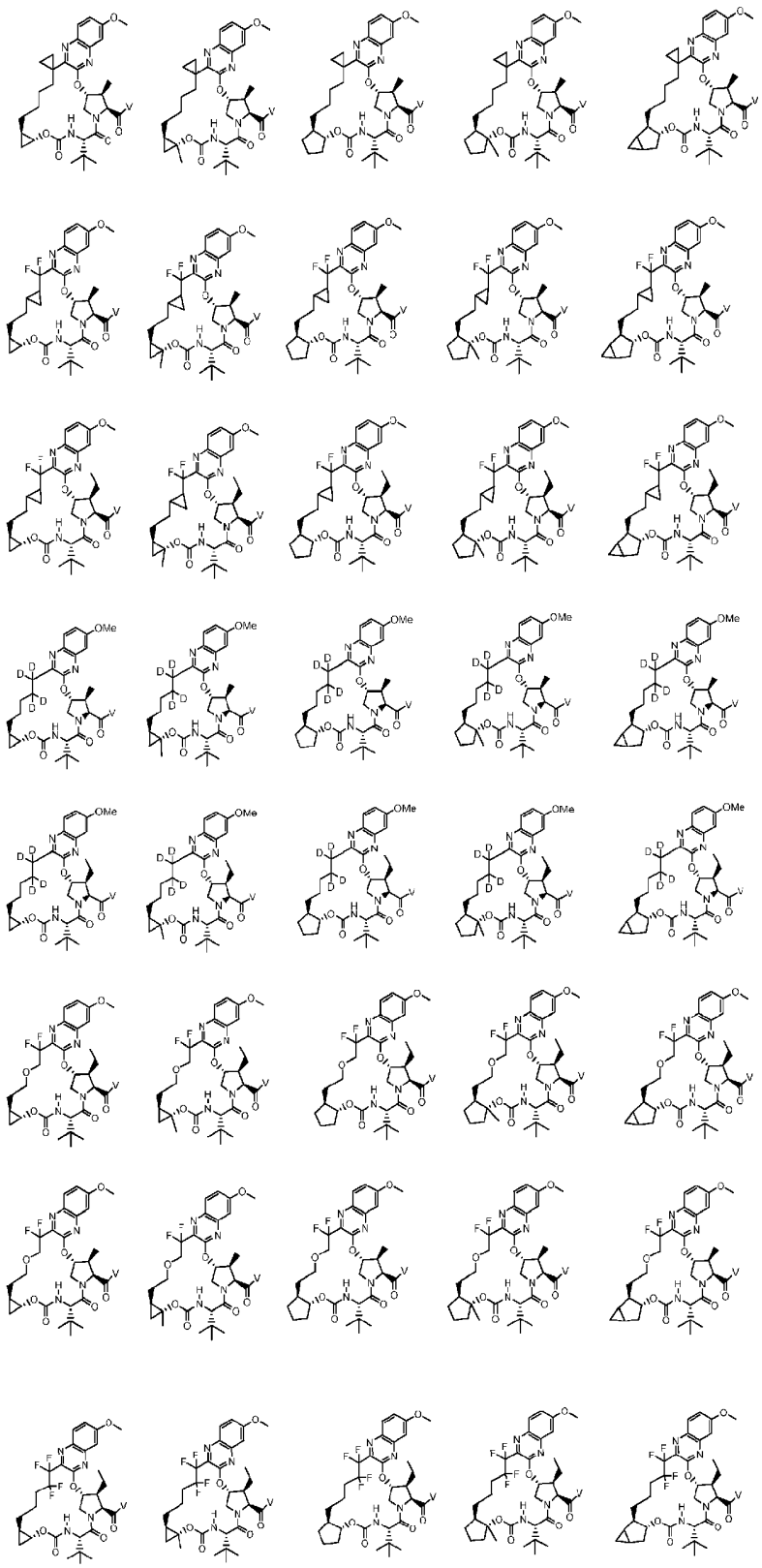


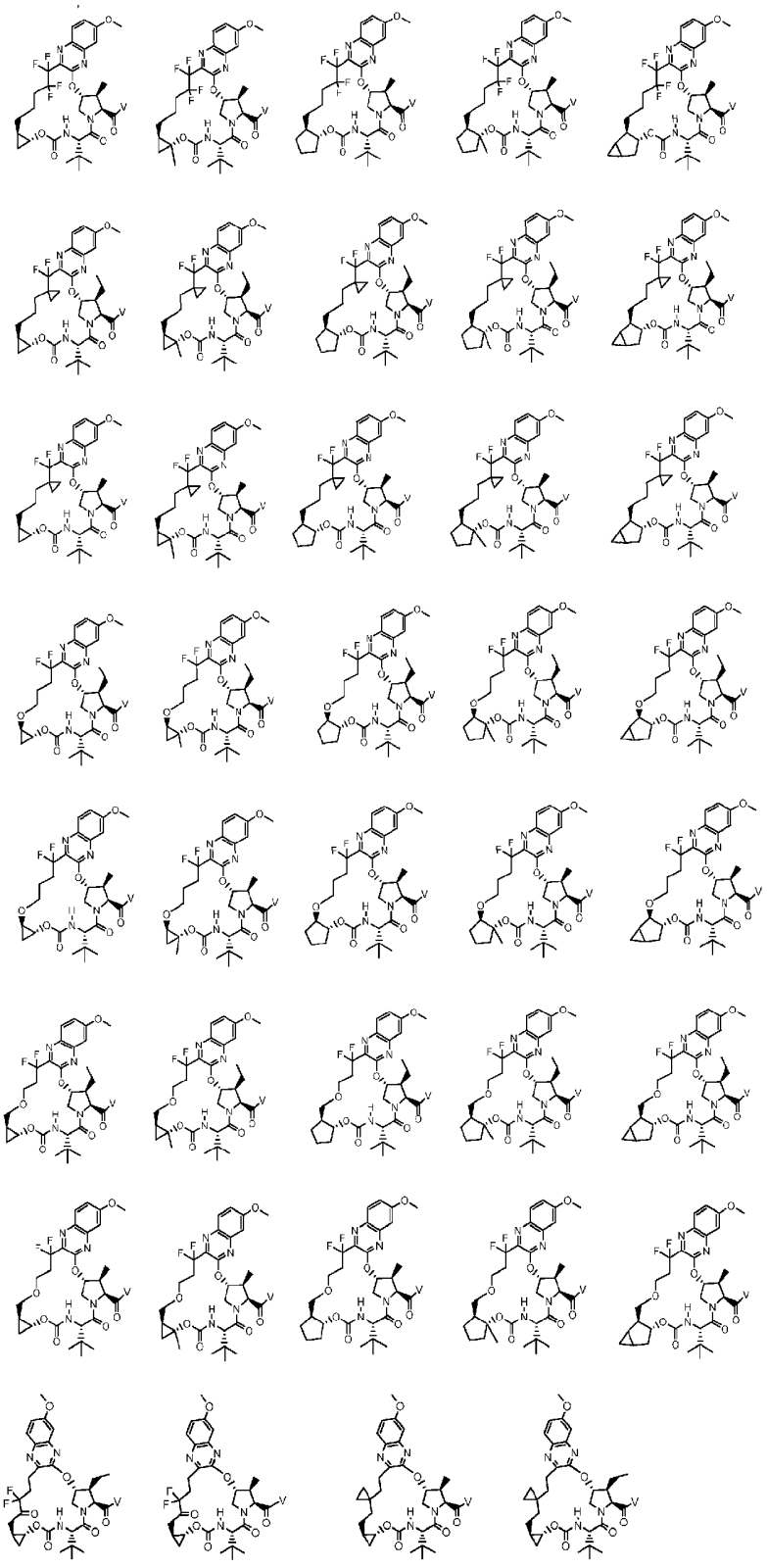


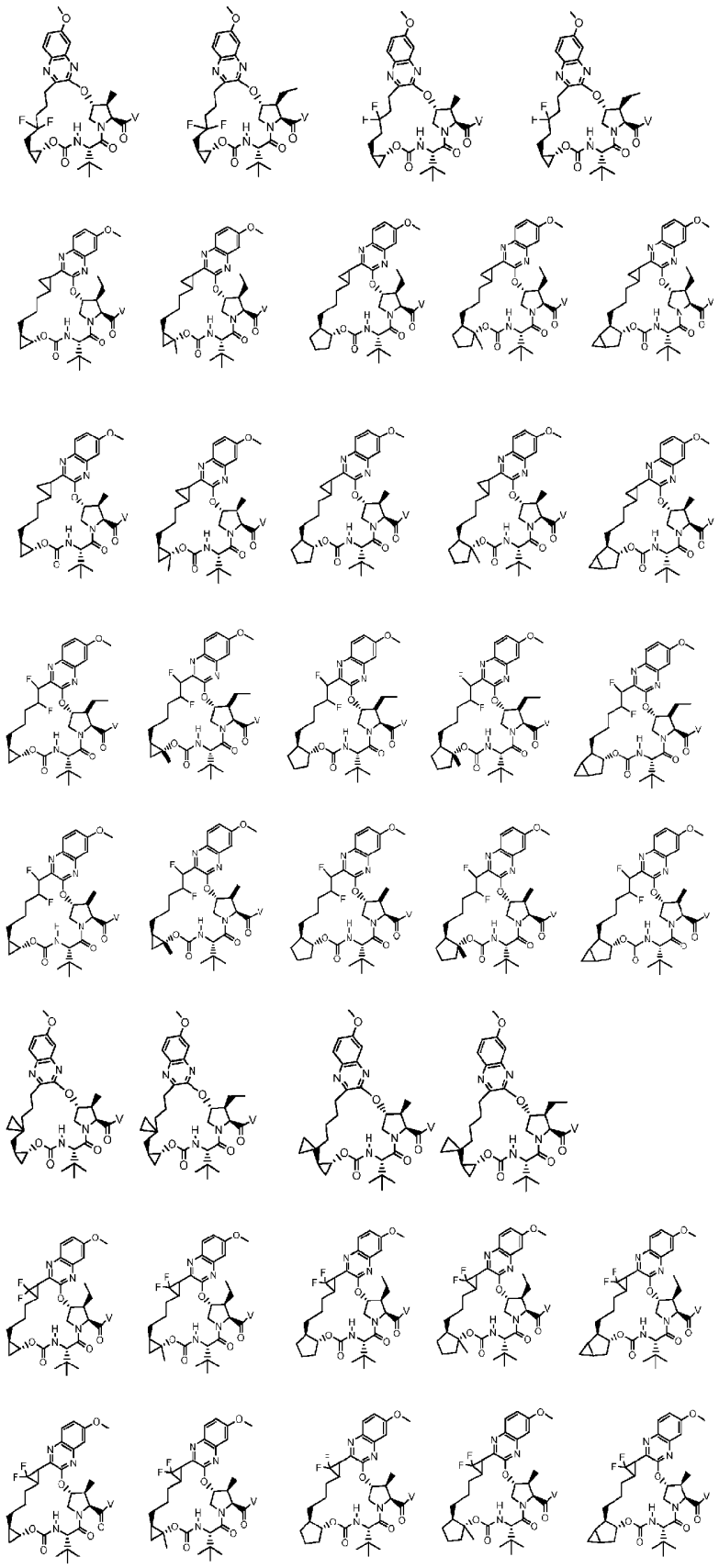


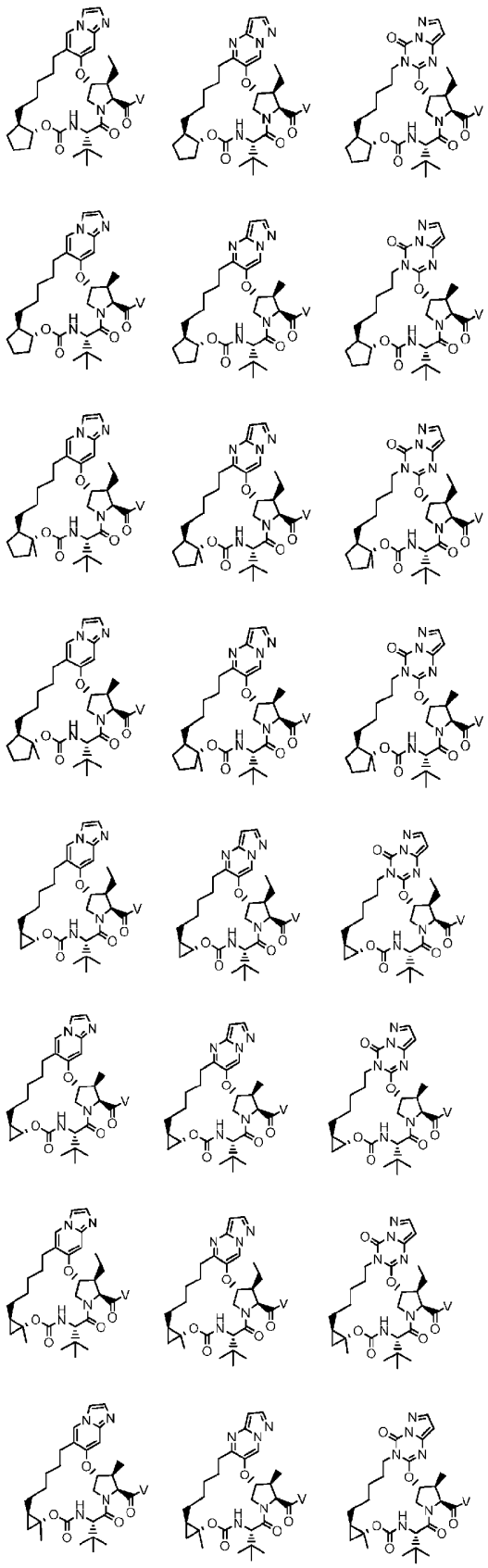


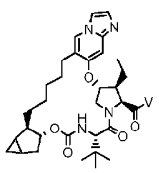
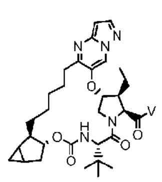
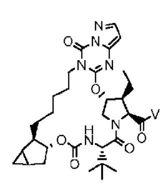


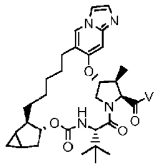
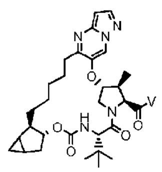
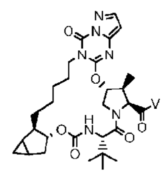


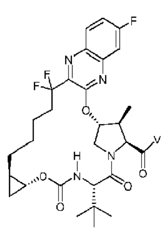
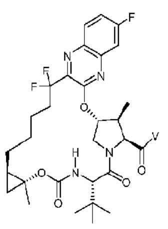
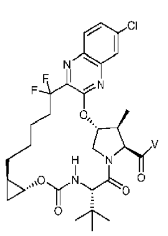
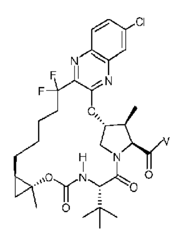


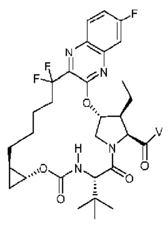
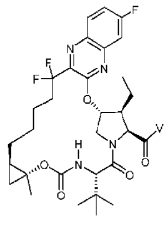
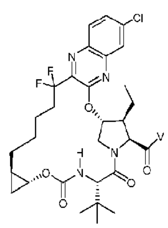
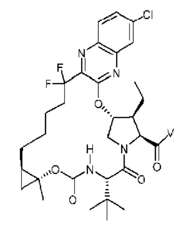


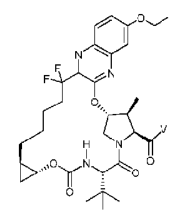
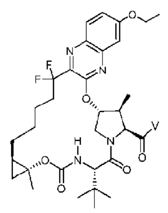
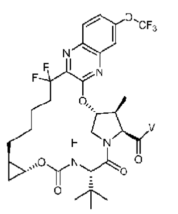
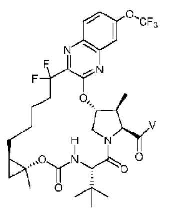


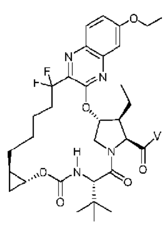
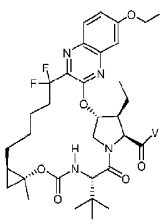
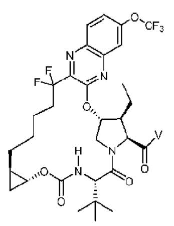
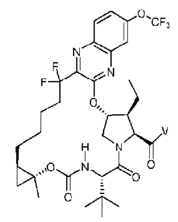




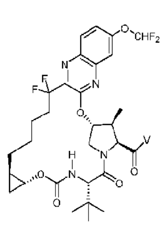
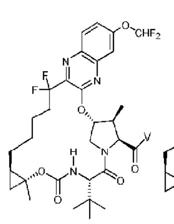
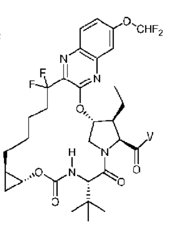
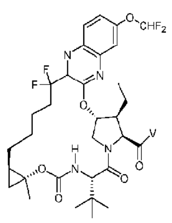




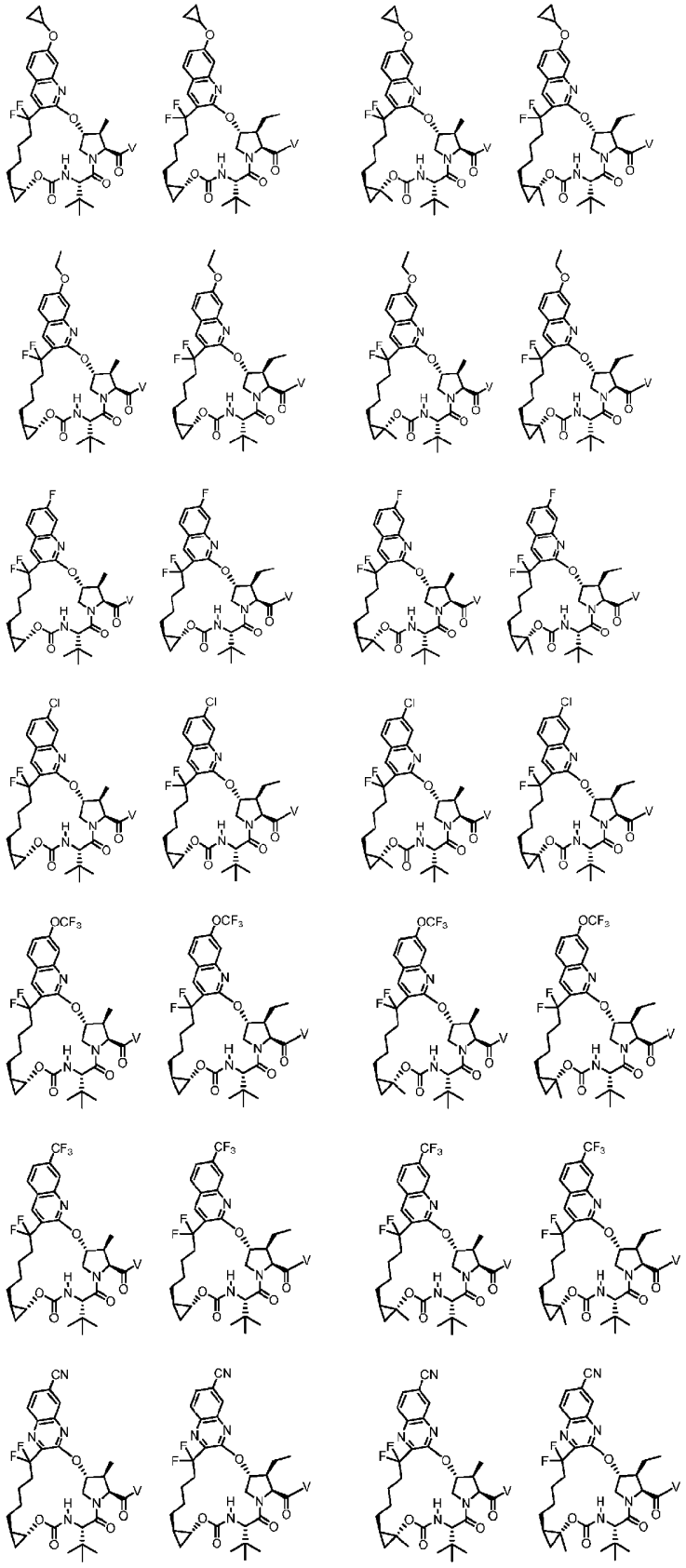





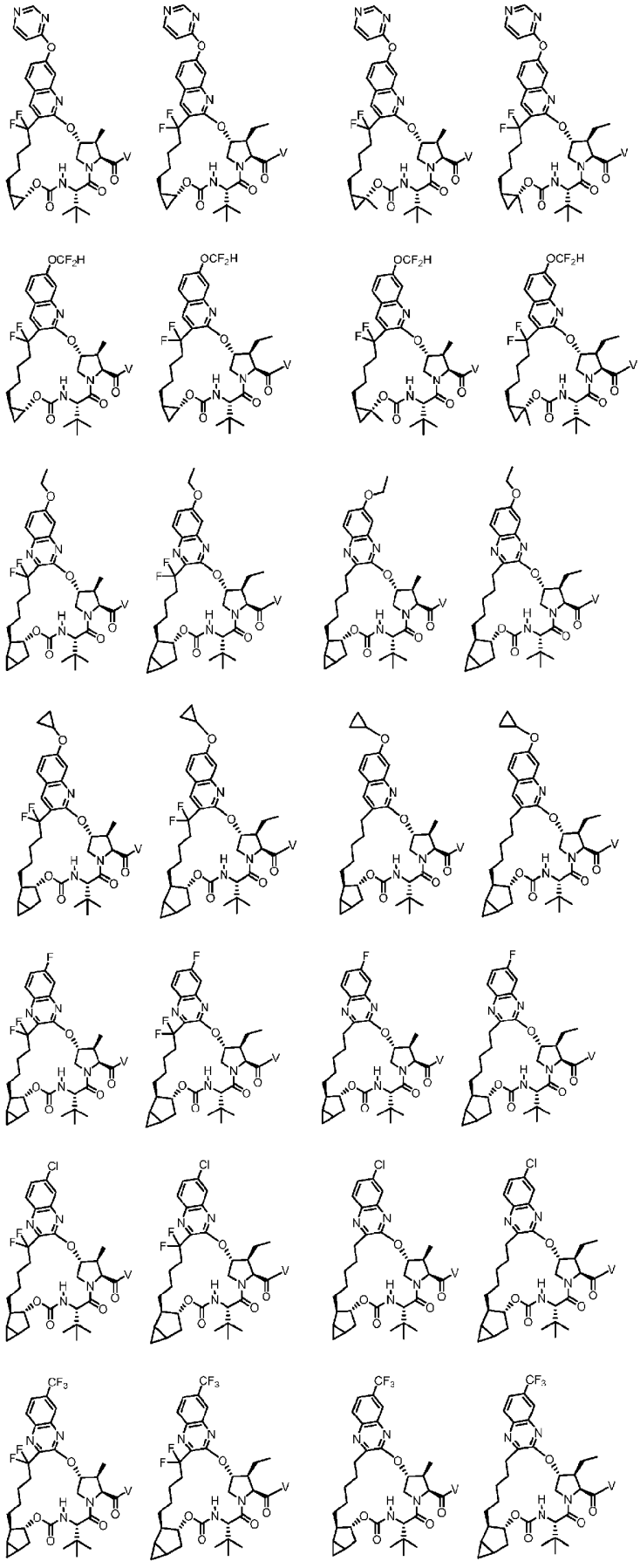





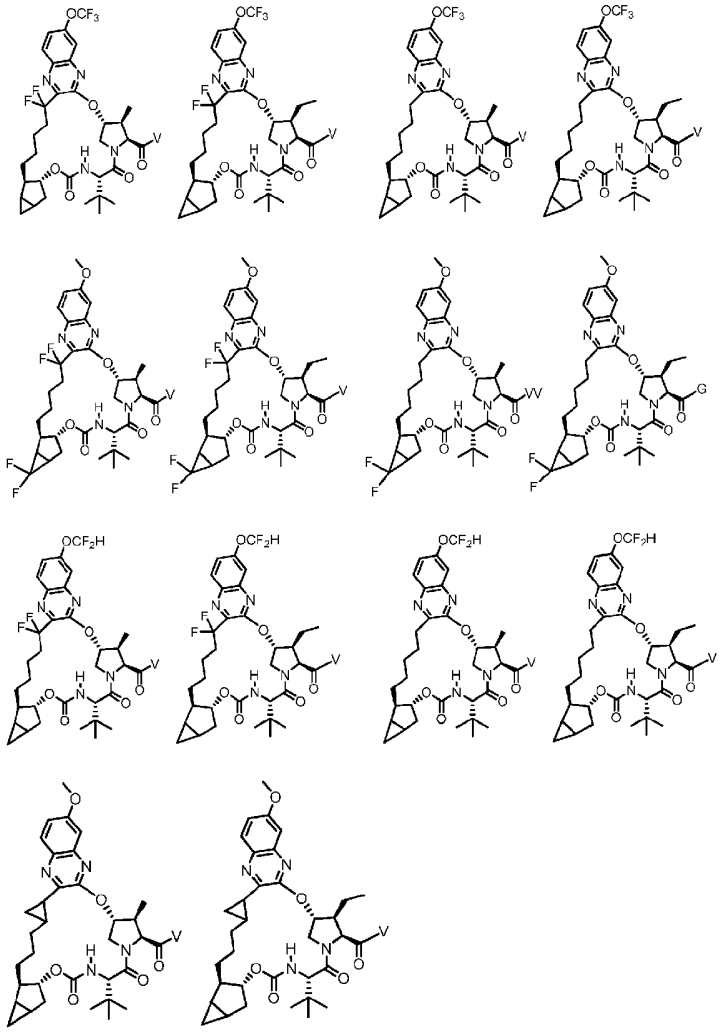





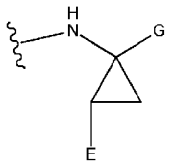











wherein V is a structure of Formula:



and wherein E and G are defined as above.

Biological Activity

Expression and Purification of Genotype 1a, 2a, and 3 NS3 Proteases **Generation of NS3 Protease Expression Plasmids**

[0330] The coding sequence of the genotype 1 b (con-1 strain) HCV NS3 protease domain was PCR amplified from a plasmid encoding the I389luc-ubi-neo/NS3-3'/ET replicon (Reblikon, Mainz, Germany). The 5'-PCR primer was designed to encode an N-terminal K_3 hexahistidine tag and to insert an in-frame recombinant Tobacco Etch virus (rTEV) protease cleavage site into the NS3 coding sequence. The resulting DNA fragment was cloned into the pET28 protein expression vector (Invitrogen, Carlsbad, CA) yielding the p28-N6H-Tev-NS3(181)1b.

[0331] The coding sequences for the genotype 3 HCV protease domain was amplified by RT-PCR using a Titan One Tube RT-PCR Kit (Roche, Indianapolis, IN) and RNA extracted from HCV-positive human serum (BBI Diagnostics, MA) using a QIAmp

UltraSens Virus Kit (Qiagen, Valencia, CA). 5' PCR primers were designed to encode N-terminal hexahistidine tags and to insert in-frame rTEV protease cleavage sites into the NS3 protease coding sequences. The resulting DNA fragments were cloned into pET28 yielding the expression vectors p28-N6H-Tev-NS3(181)1a and p28-N6H-Tev-NS3(181)3, respectively.

NS3 Protease Protein Expression

[0332] BL21AI bacteria (Invitrogen, Carlsbad, CA) were transformed with genotype 1 b or 3 NS3 expression vectors and used to inoculate a 20 L fermentation vessel (Sartorius BBI System Inc., Bethlehem, PA), containing 18 L of fresh 2YT medium supplemented with 50 µpg/mL kanamycin. When cell densities reached an OD_{600} of 1, the temperature of the cultures was reduced from 37 °C to 28 °C and induction was immediately initiated by the addition of 30 µM $ZnSO_4$, 14 mM L-arabinose and 1 mM Isopropyl β- D -thiogalactoside (IPTG) final concentrations. Cells were harvested by centrifugation four hours post-induction and were stored as frozen pellets at -80 °C prior to NS3 protein purification.

Purification of NS3 Proteases

Purification of Genotype 1b NS3 Protease

[0333] Cell pellets were thawed and resuspended at 10 mL/g cells in lysis buffer containing 50 mM tris pH 7.6, 300 mM NaCl, 0.1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS), 5% glycerol, and 2 mM β-mercaptoethanol. Cell suspensions were then sonicated, filtered through cheesecloth, and passed three times through a microfluidizer at 18,000 pounds/in^2. The resulting lysates were centrifuged at 15500 rpm for 45 minutes and supernatants were loaded onto a HisTrap HP column (GE Lifesciences) pre-equilibrated with five volumes of Ni buffer A (50 mM tris pH 7.6, 300 mM NaCl, 0.1% CHAPS, 5% glycerol, 2 mM β-mercaptoethanol, 50 mM imidazole-HCl). Proteins were eluted with a 0-100% gradient of Ni buffer A plus 500 mM imidazole-HCl and fractions were collected and pooled. The HisTrap pool was diluted 1:10 with SP-A buffer (50 mM tris pH 7.0, 10% glycerol, 2 mM dithiothreitol (DTT)) and loaded onto a HiTrap SP-HP column (GE Lifesciences) equilibrated with SP-A buffer. NS3 protease was eluted with a 0-100% SP-B buffer (SP-A buffer plus 1 M NaCl) gradient. Concentrated pools of NS3-containing SP fractions were aliquoted, snap frozen in liquid nitrogen and stored at -80° C.

Purification of Genotype 3 NS3 Protease

[0334] Bacterial pellets collected from the expression of genotype 3 HCV NS3 protease were homogenized in Lysis Buffer (25 mM tris, pH 7.5 buffer containing 150 mM NaCl and 1 mM phenylmethanesulfonyl fluoride (PMSF)) and passed through a microfluidizer at 18,000 pounds/in^2. Homogenized cell lysates were centrifuged at 30,000 x g for 30 minutes at 4° C. The resulting P1 pellets were washed with Wash Buffer I (25 mM tris, pH 7.5 containing 1% CHAPS) followed by centrifugation at 10,000 x g for 30 minutes at 4° C. The resulting P2 pellets were washed with Wash Buffer II (50 mM CAPS buffer, pH 10.8, containing 2 M NaCl and 2 M urea) followed by centrifugation at 30,000 x g for minutes at 4° C. The resulting P3 pellets were resuspended in Solubilization Buffer (20 ml of 25 mM tris, pH 7.5 containing 150 mM NaCl and 8 M urea) and incubated at 4° C for one hour. Solubilized proteins were passed through a 0.45 micron filter. Protein concentrations were measured and the solutions were adjusted to 40 mM DTT, incubated for 30 minutes at 4° C and then quickly diluted into Refolding Buffer (25 mM tris, pH 8.5, 0.8 M Guanidine-HCl, 0.4 M L-Arginine, 10 mM $ZnSO_4$) while stirring. Protein solutions were incubated at 4° C overnight to allow refolding. Refolded proteases were centrifuged at 30,000 x g for 10 minutes to remove residual precipitates. Final protein concentrations were then measured and the NS3 proteases were aliquoted, snap frozen in liquid nitrogen and stored at -80° C.

Ki Determination for Genotypes 1b and 3a NS3 Protease.

[0335] Purified NS3 protease domain (amino acids 1-181) of the genotype 1 b and 3a virus were generated as above. The internally quenched fluorogenic depsipeptide substrate Ac-DED(Edans)-EEAbuψ[COO]ASK(Dabcyl)-NH2and a synthetic peptide containing the hydrophobic core residues of the NS4A protein cofactor (KKGSVVIVGRIILSGRKK; NS4A peptide) were obtained from Anaspec, Inc. (San Jose, CA). Other chemicals and biochemicals were of reagent grade or better and were purchased from standard suppliers.

[0336] Reactions were run at room temperature in buffer consisting of 50 mM HEPES, 40% glycerol, 0.05% Triton X-100, 10 mM DTT, and 10% DMSO. The final assay solutions contained 50 pM NS3 genotype 1 b protease or 200 pM genotype 3a protease, 20 µM NS4A peptide, and 4 µM substrate (genotype 1b) or 2 µM substrate (genotype 3a). Inhibitor concentrations varied from 100 nM to 5 pM in 3-fold dilutions, and no-inhibitor controls were included.

[0337] Compound dilutions were made in DMSO at 20 x final concentration. Reaction mixtures were prepared in 96-well assay plates. A solution of enzyme and NS4A peptide in assay buffer (25 µL volume with both reagents at 4 x final concentration) was mixed with 45 µL assay buffer and 5 µL of either inhibitor or DMSO, and pre-incubated at room temperature for 1 hour. The reaction was started by addition of 25 µL substrate solution at 4 x final concentration. Plates were mixed vigorously for 5-10 seconds and reactions were allowed to proceed for 90 minutes. fluorescence was measured every 30 s between 90 and 120 minutes reaction time using a Tecan InfiniTe M1000 or PerkinElmer Envision multimode plate reader with an excitation wavelength of 340 nm and an emission wavelength of 490 nm.

[0338] Rates were calculated from the progress curves at steady state, in the time frame of 90-120 minutes after addition of substrate. To determine the K_i, rates were plotted as a function of inhibitor concentration, and the data were fit with equation 1 (Morrison, J. F., Biochimica et Biophysica Acta 1969, 185, 269-286) to calculate K_i^{app} using GraphPad Prism 5. Active fraction of enzyme was determined by active site titration with known potent inhibitors. K_i was calculated from $K_i^{app}/(1 + [[S]/K_m])$. K_i results for representative compounds for genotype 1 b and 3a (**Ki 1B** and **Ki 3A**, respectively) are reported in Table 1.

$$\frac{v}{v_0} = \frac{\bar{E}]_t - \bar{I}]_t - K_i^{app} + \sqrt{(\bar{E}_t - \bar{I}_t - K_i^{app})^2 + 4\bar{E}]_t K_i^{app}}}{2\bar{E}]_t} \qquad (1)$$

Evaluation of cell-based anti-HCV activity:

[0339] Antiviral potency (EC_{50}) was determined in both stable subgenomic HCV replicon cell lines and transient-transfected HCV replicon cells. The term half maximal effective concentration (EC_{50}) refers to the concentration of a drug which induces a response halfway between the baseline and maximum after the exposure time specified below.

[0340] Stable subgenomic HCV replicons for genotype 1 a, 1 b, 2a, 3a, and 4a were established in Huh-7-derived cells as described by Lohmann et al (Lohmann V, Korner F, Koch J, et al Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line.Science 1999; 285:119-3). Each stable cell line contains a bicistronic HCV replicon that encodes a humanized *Renilla* luciferase (hRLuc) reporter gene fused to a selectable neomycin-resistance gene, followed by an EMCV IRES and the NS3-NS5B coding region of HCV. Selection for cells constitutively expressing the HCV replicon was achieved in the presence of the selection antibiotic, neomycin (G418). Luciferase activity was measured as a marker for intracellular HCV replication levels.

[0341] The genotype 1 a stable replicon was derived from the H77 HCV strain and contained adaptive mutations P1496L and S2204I. The genotype 1 b stable replicon was derived from the Con1 HCV strain and contained adaptive mutations E1202G, T1280I, and K1846T. The genotype 2a stable replicon was derived from the JFH-1 HCV strain and did not require adaptive mutations. The genotype 3a stable replicon was derived from the S52 HCV strain and contained adaptive mutations P1121 L, A1198T and S22101 (equivalent to S2204I in genotype 1). The genotype 4a stable replicon was derived from the ED43 HCV strain and contained adaptive mutations Q1691R and S2204I. All replicon cell lines were propagated in Huh-7-derived cells and maintained in Dulbecco's modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 0.5 mg/mL G418.

[0342] Transient-transfected HCV replicons were established for genotype 1 a, 1 b, 3a and NS3/4a protease inhibitor resistant variants D168A in genotype 1 b or R155K in genotype 1a. Transient-transfected replicons are also biscistronic subgenomic replicons but do not contain the neomycin selectable marker present in stable replicons. These replicons encode the poliovirus IRES followed by the hRLuc reporter gene, the EMCV IRES and finally the NS3-NS5B coding region of HCV. The genotype 1 a (H77) and 1 b (Con1) wild-type replicons were derived from the same strain and contained the same adaptive mutations as listed above. The genotype 3a transient replicon was derived from the S52 HCV strain as above, but contained slightly different adaptive mutations P1112L, K1615E and S2210I. Specifically, the secondary adaptive mutation A1198T (A166T) in the protease domain of the stable genotype 3a replicon was replaced with K1615E (K583E) in the NS3 helicase, with no effect on replication efficiency. Removal of A166T located in the protease domain minimizes the impact of this variant on inhibitors targeting the protease domain and represents a protease domain closer to wild type for genotype 3a. Resistant replicons encoding NS3/4

protease inhibitor mutations were introduced into the 1 b or 1 a wild-type NS3 gene by site directed mutagenesis. In vitro transcribed RNAs from all transient replicons were transfected into naive Huh-7-derived cell lines by electroporation. Luciferase activity was measured as a marker for intracellular HCV replication levels

[0343] To perform EC_{50} assays, cells from each HCV replicon were dispensed into 384-well plates. Compounds were dissolved in DMSO at a concentration of 10 mM and diluted in DMSO using an automated pipetting instrument. Threefold serially diluted compounds were directly added to the cells using an automated instrument. DMSO was used as a negative (solvent; no inhibition) control, and a combination of three HCV inhibitors including a protease inhibitor; an NS5A inhibitor and a nucleoside inhibitor was used at concentrations > 100 x EC_{50} as a positive control (100% inhibition). Seventy-two hours later, cells were lysed and *Renilla* luciferase activity were quantified as recommended by the manufacturer (Promega-Madison, WI). Non-linear regression was performed to calculate EC_{50} values.

Results are shown in Tables 1 and 2:

[0344]

Table 1: Biological Activity Values For Stable Subgenonic HCV Replicon Cell Lines

Example	Ki 1B (nM)	Ki 3A (nM)	EC_{50} 1A RLUC* (nM)	EC_{50} 1B RLUC* (nM)	EC_{50} 2A RLUC* (nM)	EC_{50} 3A RLUC* (nM)	EC_{50} 4A RLUC* (nM)
1	0.03	0.07	4.4	3.9	4.1	46	3.1
2	0.01	0.04	4.0	3.1	3.9	77	2.7
3	0.18	0.56	11.7	9.8	28	546	10
4	0.17	0.56	10.7	9.6	16	271	7.9
5	0.04	0.17	8.7	7.4	11	405	6.9
6	0.20	0.62	35	36	34	1361	34
7	0.05	0.06	4.9	3.8	4.2	67	3.2
8	0.07	0.42	16	8.6	20	465	13
9	0.15	0.59	17	7.9	23	1268	11
10	0.16	0.52	30	22	49	978	26
11	0.23	0.88	28	17	34	1162	19
12	0.27	1.2	34	18	25	2013	21
13	0.04	0.18	13	9.5	26	685	11
14	0.07	0.24	9.7	6.8	7.0	308	7.3
15	0.05	0.30	11	6.8	9.8	550	7.8
16	0.09	0.21	12	7.4	6.2	201	8.1
17	0.04	0.06	3.9	3.3	3.7	15	2.9
18	0.03	0.10	3.9	2.6	5.0	70	2.8
19	0.02	0.13	4.0	2.6	4.6	89	3.1
20	0.12	0.53	8.1	5.2	19	392	5.9
21	0.10	0.45	6.8	4.7	12	263	6.2
22	0.07	1.3	15	7.5	27	727	11
23	0.08	1.1	13	7.5	23	587	9.9
24	0.05	0.92	12	7.5	20	663	9.2
25	0.05	0.39	8.8	6.3	13	409	7.1
26	0.05	0.17	6.3	4.3	12	297	6.0
27	0.03	0.08	6.6	5.2	6.7	266	6.1
28	0.03	0.08	6.7	4.6	6.2	266	4.1

Example	Ki 1B (nM)	Ki 3A (nM)	EC_{50} 1A RLUC* (nM)	EC_{50} 1B RLUC* (nM)	EC_{50} 2A RLUC* (nM)	EC_{50} 3A RLUC* (nM)	EC_{50} 4A RLUC* (nM)
29	0.06	0.12	10	8.9	11	137	7.2
30	0.14	0.63	55	35	47	2437	31
31	0.13	4.9	40	18	63	2071	20
32	0.18	0.87	59	30	35	2311	30
33	0.03	0.06	7.6	2.8	4.9	16	2.3
34	0.10	0.28	12	13	18	322	9.7
35	0.07	0.23	9.1	11	7.4	162	7.6
36	0.10	1.7	23	14	53	585	9.1
37	0.10	0.19	24	22	16	575	15
38	0.03	0.70	7.8	4.2	5.4	151	5.5
39	0.08	0.20	34	39	41	321	26
40	0.08	0.18	25	22	48	360	18
41	0.18	0.79	135	142	106	2606	135
42	0.10	0.75	20	16	17	343	14
43	0.06	0.16	4.9	3.8	5.2	92	3.6
44	0.03	0.08	3.1	2.1	2.9	53	2.2
45	0.04	0.48	21	8.3	24	549	13
46	0.03	0.05	3.1	2.7	3.8	17	2.5
47	0.07	0.19	3.8	3.6	12	58	4.2
48	0.07	0.09	2.0	1.8	9.7	73	2.2
49	0.04	0.07	3.7	4.1	5.2	20	3.5
50	63	100	4444	4444	379	19708	4444
51	0.31	0.84	40	39	103	1221	30
52	0.25	1.3	195	245	380	2307	161
53	0.03	0.09	51	7.7	13	18	2.8
54	0.11	0.50	33	18	76	260	13
55	0.09	0.20	13	3.8	12	140	3.5
56	0.38	1.0	41	37	57	1026	57
57	0.07	0.28	12	11	21	166	4.9
58	0.07	0.17	12	9.7	12	134	12
59	0.04	0.06	5.4	11	13	20	5.6
60	0.04	0.08	11	4.8	7.7	45	5.4
61	0.06	0.09	13	10	8.7	28	11
62	0.04	0.03	3.4	3.0	5.0	8.5	2.4
63	0.03	0.01	4.2	2.9	3.2	11	3.2
64	0.07	1.2	100	38	48	671	34
65	0.08	0.07	12	8.4	7.7	30	8.1
66	0.04	0.06	37	20	105	1786	25
67	0.04	0.32	11	12	24	383	12
68	0.05	0.63	13	7.7	18	364	9.4
69	0.07	0.17	5.2	4.9	11	64	5.8

Example	Ki 1B (nM)	Ki 3A (nM)	EC_{50} 1A RLUC* (nM)	EC_{50} 1B RLUC* (nM)	EC_{50} 2A RLUC* (nM)	EC_{50} 3A RLUC* (nM)	EC_{50} 4A RLUC* (nM)
70	0.05	0.05	8.4	8.5	15	41	6.4
71	0.03	0.14	6.5	5.3	23	160	5.3
72	0.05	4.1	365	300	740	1819	383
73	0.11	0.82	7.9	7.5	22	178	7.2
74	0.03	0.12	8.0	5.0	18	374	8.3
75	0.03	0.12	9.9	6.4	18	240	10
76	0.03	0.06	2.4	2.2	2.4	9.0	1.9
77	nt	nt	23	12	29	741	16
78	0.21	0.82	267	394	195	1115	225
79	0.06	0.06	7.0	5.8	4.1	71	5.6
80	0.49	13	1127	344	748	44444	1182
81	0.04	0.05	4.0	3.6	3.6	12	4.3
82	0.03	0.04	8.5	9.3	4.7	25	10
83	0.09	0.48	62	58	19	1219	42
84	0.04	0.08	5.9	5.7	7.2	27	6.4
85	0.05	0.03	16	17	7.7	304	9.2
86	0.04	0.07	5.6	5.5	5.9	42	5.7
87	0.02	0.05	4.8	3.9	3.3	14	3.8
88	0.02	0.29	9.3	4.6	2.7	105	4.1
89	0.03	0.05	6.0	6.1	4.3	19	4.6
90	0.06	0.13	12	9.6	8.8	114	10.4
91	nt	nt	2.4	1.9	4.0	149	2.4
92	nt	nt	3.3	3.2	4.6	58	3.2
93	nt	nt	12	14	15	116	11
94	nt	nt	3.8	5.2	3.3	32	3.0
96	nt	nt	12	11	5.4	77	8.9
97	nt	nt	6.3	4.6	5.8	67	5.3

nt - not tested
*RULC: *Renilla* luciferase

Table 2: Biological Activity Values For Transient-Transfected HCV Replicon Cell Lines

	EC_{50} 3A WT* (nM)	EC_{50} 1A WT* (nM)	EC_{50} 1A R155K† (nM)	EC_{50}1B WT* (nM)	EC_{50}1B D168A‡ (nM)
1	17	3.2	4.9	2.2	17
2	nt	2.4	7.0	1.0	33
3	nt	6.6	32	3.5	128
4	68	7.1	20	6.5	66
5	nt	3.7	17	3.2	91
6	nt	26	58	11	216
7	14	3.8	6.7	2.3	20
8	nt	8.8	28	4.8	89
9	nt	12	208	2.5	360
10	nt	37	131	10	493

	EC_{50} 3A WT* (nM)	EC_{50} 1A WT* (nM)	EC_{50} 1A R155K† (nM)	EC_{50}1B WT* (nM)	EC_{50}1B D168A‡ (nM)
11	nt	20	159	9.4	605
12	nt	14	283	5.7	640
13	nt	8.6	59	3.1	209
14	nt	7.4	21	4.0	99
15	nt	6.5	20	3.0	182
16	nt	9.4	22	5.8	61
17	6.1	2.9	2.8	1.7	4.3
18	nt	2.3	5.0	1.2	24
19	nt	2.1	3.4	1.1	28
20	Nt	3.4	17	2.7	90
21	nt	4.1	15	3.8	70
22	nt	8.6	48	2.6	242
23	nt	9.5	36	3.6	173
24	nt	9.3	49	3.2	284
25	nt	4.4	17	3.6	116
26	nt	3.6	12	1.9	109
27	nt	6.0	20	4.3	70
28	nt	3.0	9	3.4	54
29	nt	4.8	11	3.1	48
30	nt	41	296	31	503
31	nt	27	154	6.6	805
32	nt	44	547	14	653
33	5.3	2.6	2.5	1.6	4.2
34	46	15	18	9	64
35	35	12	17	10	38
36	128	16	271	9.4	333
37	69	29	51	22	159
38	nt	4.5	8.4	2.8	25
39	89	23	63	16	105
40	156	17	74	8.6	129
41	539	164	505	154	715
42	nt	17	35	10	109
43	nt	3.8	8.7	2.4	41
44	7.0	2.4	4.0	1.4	15
45	nt	13	35	5.3	88
46	6.788	2.4	3.2	1.2	4.5
47	17	5.4	6.1	2.0	12
48	13	1.7	4.0	1.1	6.5
49	6.3	3.5	3.8	2.8	4.2
50	26825	4444	3830	4444	4444
51	265	28	92	24	318

	EC_{50} 3A WT* (nM)	EC_{50} 1A WT* (nM)	EC_{50} 1A R155K† (nM)	EC_{50}1B WT* (nM)	EC_{50}1B D168A‡ (nM)
52	538	150	516	161	887
53	15	5.3	5.6	2.0	11
54	147	19	27	10	123
55	71	8.0	32	2.3	53
56	226	63	168	59	252
57	54	12	17	7.5	48
58	38	12	18	14	23
59	15	10	6.8	6.8	6.4
60	9.8	5.8	8.6	2.3	15
61	13	12	10	9.3	6.7
62	4.0	3.5	2.7	1.5	2.0
63	6.9	4.1	4.0	2.1	3.4
64	256	37	50	17	104
65	17	9.4	8.1	6.4	11
66	735	35	240	14	396
67	107	14	42	10	86
68	139	14	37	4.4	78
69	42	8.2	15	3.9	28
70	17	7.7	5.4	6.1	7.3
71	49	9.1	30	3.8	66
72	642	600	227	165	687
73	45	8.8	25	6.2	75
74	138	8.8	44	2.1	56
75	56	14	45	3.5	51
76	3.4	2.0	2.1	1.0	2.8
77	472	21	34	5.0	80
78	194	189	225	156	248
79	9.2	6.1	7.1	3.0	11
80	nt	403	2862	53	443
81	4.3	3.7	2.5	2.4	2.7
82	16	7.8	6.2	4.1	5.7
83	300	62	133	27	202
84	11	5.4	4.0	2.5	5.2
85	101	12	22	7.0	57
86	16	4.0	3.7	3.4	10
87	7.7	2.9	2.8	1.3	4.0
88	35	5.0	14	5.5	24
89	5.5	6.0	3.7	3.2	5.1
90	43	nt	nt	nt	nt
91	25	2.3	3.5	1.3	9.2
92	8.0	3.0	3.0	1.7	5.3

	EC_{50} 3A WT* (nM)	EC_{50} 1A WT* (nM)	EC_{50} 1A R155K† (nM)	EC_{50}1B WT* (nM)	EC_{50}1B D168A‡ (nM)
93	26	13	13	14	39
94	10	3.2	3.1	1.9	9.2
96	12	5.2	3.8	4.1	3.6
97	5.8	3.6	3.7	2.5	8.8

nt: not tested
*WT = wild type
† NS3/4a protease inhibitor resistant variants R155K in genotype 1 a
‡ NS3/4a protease inhibitor resistant variants D168A in genotype 1 b

[0345] The data in Tables 1 and 2 represent an average over time of each assays for each compound. For certain compounds, multiple assays have been conducted over the life of the project. Thus, the data reported in Tables 1 and 2 include the data reported in the priority document, as well as data generated in the intervening period.

Pharmaceutical Compositions

[0346] The following illustrate representative pharmaceutical dosage forms, containing a compound of Formulas I, II, III, or IV (such as any one of IVa-IVh) ('Compound X'), for therapeutic or prophylactic use in humans.

(i) Tablet 1	mg/tablet
Compound X=	100.0
Lactose	77.5
Povidone	15.0
Croscarmellose sodium	12.0
Microcrystalline cellulose	92.5
Magnesium stearate	3.0
	300.0

(ii) Tablet 2	mg/tablet
Compound X=	20.0
Microcrystalline cellulose	410.0
Starch	50.0
Sodium starch glycolate	15.0
Magnesium stearate	5.0
	500.0

(iii) Capsule	mg/capsule
Compound X=	10.0
Colloidal silicon dioxide	1.5
Lactose	465.5
Pregelatinized starch	120.0
Magnesium stearate	3.0
	600.0

(iv) Injection (1 mg/ml)	mg/ml
Compound X= (free acid form)	1.0
Dibasic sodium phosphate	12.0
Monobasic sodium phosphate	0.7

(iv) Injection (1 mg/ml)	mg/ml
Sodium chloride	4.5
1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

[0347] The above formulations may be obtained by conventional procedures well known in the pharmaceutical art.

[0348] The use of the terms "a" and "an" and "the" and similar references in the context of this disclosure (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context.

[0349] The use of individual numerical values is stated as approximations as though the values were preceded by the word "about" or "approximately." Similarly, the numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about" or "approximately." In this manner, variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. As used herein, the terms "about" and "approximately" when referring to a numerical value shall have their plain and ordinary meanings to a person of ordinary skill in the art to which the disclosed subject matter is most closely related or the art relevant to the range or element at issue. The amount of broadening from the strict numerical boundary depends upon many factors. For example, some of the factors which may be considered include the criticality of the element and/or the effect a given amount of variation will have on the performance of the claimed subject matter, as well as other considerations known to those of skill in the art. As used herein, the use of differing amounts of significant digits for different numerical values is not meant to limit how the use of the words "about" or "approximately" will serve to broaden a particular numerical value or range. Thus, as a general matter, "about" or "approximately" broaden the numerical value. Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values plus the broadening of the range afforded by the use of the term "about" or "approximately." Thus, recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein.

REFERENCES CITED IN THE DESCRIPTION

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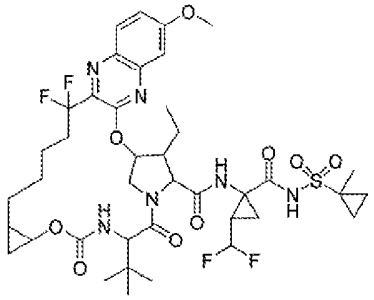
HÆMMERE AF HEPATITIS C-VIRUS

PATENTKRAV

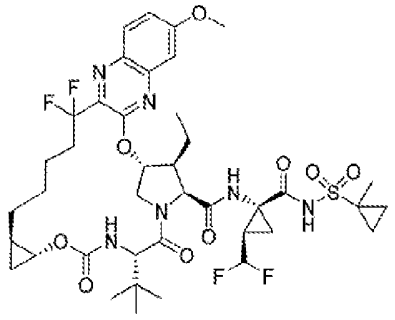
1. Forbindelse med formel IVa:



(IVa)

eller et farmaceutisk acceptabelt salt deraf.

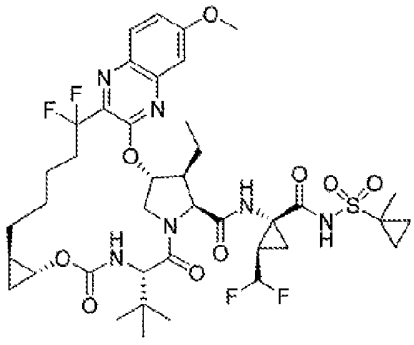
2. Forbindelse ifølge krav 1, der er en forbindelse med formel IVb:



(IVb)

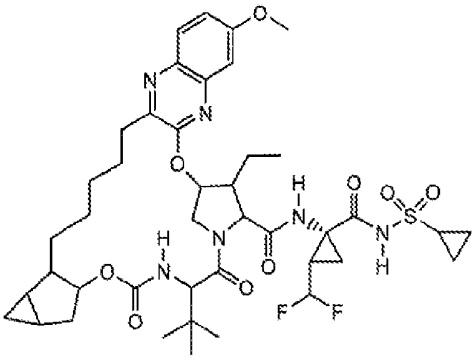
eller et farmaceutisk acceptabelt salt deraf.

3. Forbindelse ifølge krav 1, der er en forbindelse med formel IVb:



(IVb).

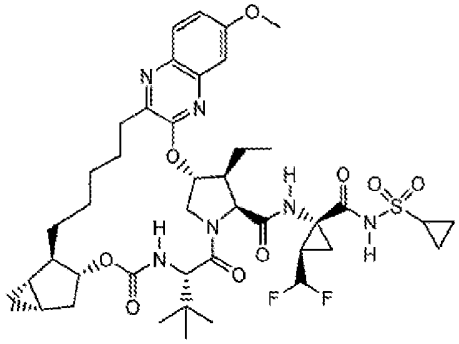
4. Forbindelse med formel IVc:



(IVc)

eller et farmaceutisk acceptabelt salt deraf.

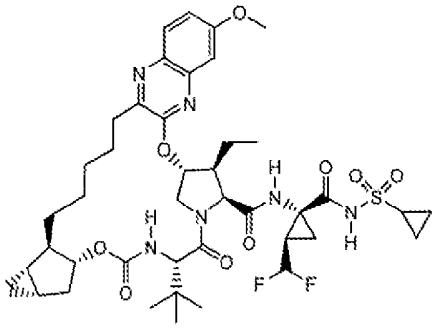
5. Forbindelse ifølge krav 4, der er en forbindelse med formel IVd:



(IVd)

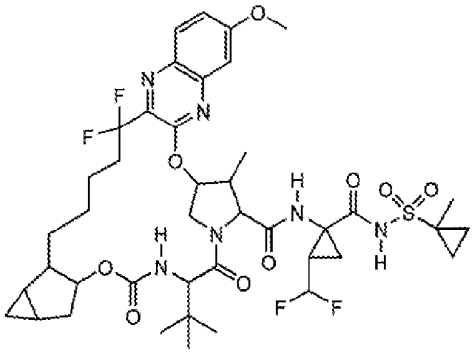
eller et farmaceutisk acceptabelt salt deraf.

6. Forbindelse ifølge krav 4, der er en forbindelse med formel IVd:



(IVd).

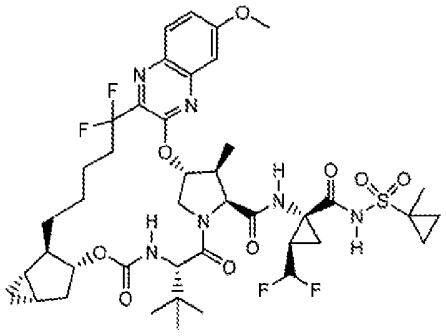
7. Forbindelse med formel IVe:



(IVe)

eller et farmaceutisk acceptabelt salt deraf.

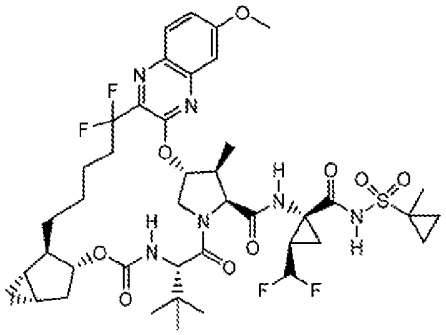
8. Forbindelse ifølge krav 7, der er en forbindelse med formel IVf:



(IVf)

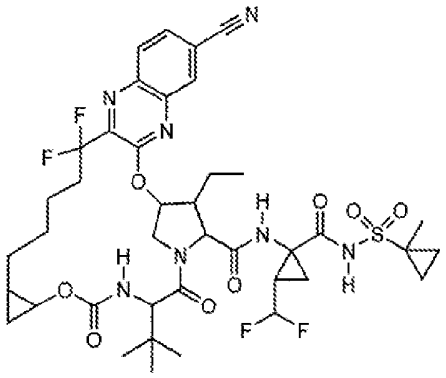
eller et farmaceutisk acceptabelt salt deraf.

9. Forbindelse ifølge krav 7, der er en forbindelse med formel IVf:



(IVf)

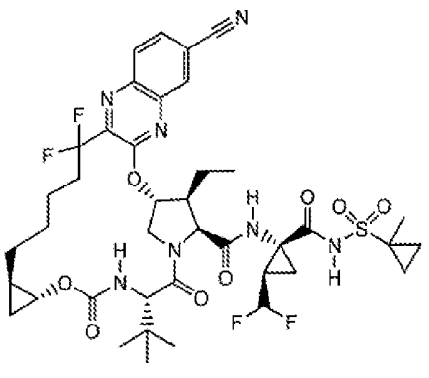
10. Forbindelse med formel IVg:



(IVg)

eller et farmaceutisk acceptabelt salt deraf.

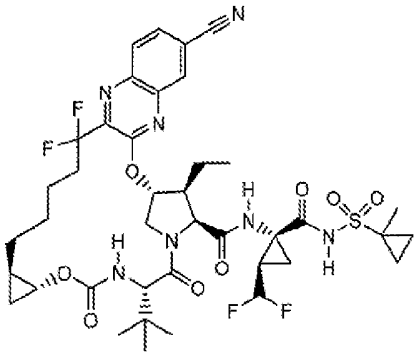
11. Forbindelse ifølge krav 10, der er en forbindelse med formel IVh:



(IVh)

eller et farmaceutisk acceptabelt salt deraf.

12. Forbindelse ifølge krav 10, der er en forbindelse med formel IVh:



(IVh).

13. Farmaceutisk sammensætning, der omfatter en forbindelse ifølge et hvilket som helst af kravene 1-12, eller et farmaceutisk acceptabelt salt deraf, og et farmaceutisk acceptabelt excipiens.

14. Forbindelse ifølge et hvilket som helst af kravene 1 til 12, eller et farmaceutisk acceptabelt salt deraf til anvendelse i medicinsk terapi.

15. Farmaceutisk sammensætning ifølge krav 13 til anvendelse til behandling af hepatitis C-virusinfektion.

16. Forbindelse ifølge et hvilket som helst af kravene 1 til 12 eller et farmaceutisk acceptabelt salt deraf til anvendelse i den profylaktiske eller terapeutiske behandling af en hepatitis C-virusinfektion.