# MACROCYCLIC ALPHA4BETA7 INTEGRIN INHIBITORS

## INTRODUCTION

**[0001]** The present invention relates to compounds that inhibit the binding of the integrin receptor α4β7 to the mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and show selectivity over the closely related integrin receptor α4β1. The present invention also relates to processes for the preparation of these compounds, to pharmaceutical compositions comprising them, and to their use in the treatment of diseases or disorders associated with α4β7, such as inflammatory bowel disease, including ulcerative colitis and Crohn's disease.

## BACKGROUND OF THE INVENTION

**[0002]** Integrins are a family of transmembrane adhesion receptors, that facilitate the adhesive connection between cells and their surrounding extracellular matrix or neighbouring cells (DOI: 10.1007/s00441-009-0834-6; DOI: 10.1016/j.bbamem.2020.183206). They comprise of heterodimeric Type I transmembrane proteins consisting of two non-covalently associated subunits, one alpha (α) subunit and one beta (β) subunit (DOI: 10.5483/bmbrep.2014.47.12.241). These subunits contain a large extracellular domain, a single transmembrane domain, and a short cytoplasmic tail (DOI: 10.1242/jcs.01014). The globular head domain creates a binding site for extracellular ligands while the short cytoplasmic tails interact with a cluster of associated proteins that ultimately connects to the cytoskeleton. In mammals, there are 18 known alpha subunits and eight known beta subunits, which combine to form 24 distinct integrin receptors that play an important role in numerous biological processes including leukocyte migration (DOI: 10.1242/jcs.01014; DOI: 10.1016/s0092-8674(02)00971-6). This is regulated by two mechanisms: first, by the differential expression of integrins, and second, by chemokines that induce changes in integrin adhesive state (DOI: 10.1038/346425a). This allows different leukocyte populations to be recruited to specific organs in response to different inflammatory signals which, if left unchecked, can lead to chronic inflammation and autoimmune disease (DOI: 10.1007/978-88-470-2143-3_5).

**[0003]** The α4β7 integrin receptor, which is highly expressed on lymphocytes, including B and T lymphocytes, directs the homing of lymphocytes to the intestine via binding to its primary ligand, MAdCAM-1, which is expressed predominantly on intestinal endothelial cells (DOI: 10.1046/j.1365-2567.1996.d01-706.x; DOI: 10.4049/jimmunol.0902407; DOI: 10.1111/j.1365-2567.2005.02225.x PMCID: PMC1857942). Therefore, inhibiting α4β7 from binding to MAdCAM-1 may be a useful method for treating inflammatory conditions of the intestine. Indeed, monoclonal antibodies displaying high binding affinity for α4β7, for example

Natalizumab (Tysabri®) and Vedolizumab (Entyvio®), have displayed therapeutic benefits for gastrointestinal autoinflammatory/autoimmune diseases, such as ulcerative colitis and Crohn's disease (DOI: 10.1056/NEJMoa1215734; DOI: 10.1056/NEJMoa1215739). However, there are potential concerns regarding the long-term administration of these therapies. For example, immunogenicity, which leads to a decrease in the effectiveness of drugs and an increase in the risk of hypersensitivity reactions due to the development of persistent anti-drug antibodies (DOI: 10.3748/wjg.v24.i17.1868; DOI: 10.3109/08830185.2012.690794; DOI: 10.1038/ni1275; DOI: 10.1016/j.jns.2008.08.003). Also, these therapies are administered by injection which can result in infusion-related reactions (DOI: 10.1016/j.msard.2019.101523). Furthermore, one of these therapies, Natalizumab, also inhibits $\alpha 4\beta 1$ integrin-ligand interactions, which carries an increased risk of development of progressive multifocal leukoencephalopathy (PML), an opportunistic brain infection caused by reactivated John Cunningham virus, which usually leads to death or severe disability (DOI: 10.1111/j.1527-3458.2007.00003.x).

**[0004]** Therefore, the development of an effective and safe small molecule α4β7 integrin inhibitor that can be administered orally, potentially increasing patient drug adherence, would be an important addition to the therapeutic armamentarium for α4β7 mediated conditions, such as the inflammatory bowel diseases ulcerative colitis, and Crohn's disease. Indeed, clinical studies are ongoing with two selective small molecule α4β7 integrin inhibitors (NCT05291689; ACTRN12621000612819).

**[0005]** Therefore, there is an ongoing need for development of an effective and safe small molecule α4β7 integrin inhibitor, given the role of α4β7 in inflammatory bowel diseases.

## SUMMARY OF THE INVENTION

**[0006]** In one aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof as defined herein.

**[0007]** In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

**[0008]** In another aspect, the present invention relates to a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in therapy.

**[0009]** In another aspect, the present invention relates to a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of diseases or disorders mediated by α4β7.

**[0010]** In another aspect, the present invention relates to a method of treating a disease or disorder mediated by α4β7, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

**[0011]** Examples of diseases or disorders mediated by α4β7 include inflammatory bowel disease, including ulcerative colitis and Crohn's disease.

**[0012]** In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of inflammatory bowel disease, including ulcerative colitis and Crohn's disease.

**[0013]** In another aspect, the present invention provides a method of treating inflammatory bowel disease, including ulcerative colitis and Crohn's disease, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

**[0014]** The present invention further provides a method of synthesising a compound, or a pharmaceutically acceptable salt thereof, as defined herein.

**[0015]** In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, obtainable by, or obtained by, or directly obtained by a method of synthesis as defined herein.

**[0016]** In another aspect, the present invention provides novel intermediates as defined herein which are suitable for use in any one of the synthetic methods set out herein.

**[0017]** Preferred, suitable, and optional features of any one particular aspect of the present invention are also preferred, suitable, and optional features of any other aspect.

## DETAILED DESCRIPTION OF THE INVENTION

### Definitions

**[0018]** Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

**[0019]** It is to be appreciated that references to "treating" or "treatment" include prophylaxis as well as the alleviation of established symptoms of a condition. "Treating" or "treatment" of a state, disorder or condition therefore includes: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a human that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or

display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, *i.e.*, arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving or attenuating the disease, *i.e.*, causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

**[0020]** A “therapeutically effective amount” means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

**[0021]** In this specification the term “alkyl” includes both straight and branched chain alkyl groups. References to individual alkyl groups such as “propyl” are specific for the straight chain version only and references to individual branched chain alkyl groups such as “isopropyl” are specific for the branched chain version only. For example, “(1-6C)alkyl” includes (1-4C)alkyl, (1-3C)alkyl, propyl, isopropyl and *t*-butyl. A similar convention applies to other radicals, for example “phenyl(1-6C)alkyl” includes phenyl(1-4C)alkyl, benzyl, 1-phenylethyl and 2-phenylethyl.

**[0022]** In this specification the term “alkylene” includes both straight and branched chain divalent alkyl groups. For example, “$C_{1-4}$alkylene” includes methylene (-$CH_2$-), ethylene (-$CH_2CH_2$-), propylene and butylene.

**[0023]** In this specification the term “alkoxy” includes both straight and branched chain alkyl groups singularly bonded to oxygen. For example, “$C_{1-4}$alkoxy” includes methoxy, ethoxy, isopropoxy and *t*-butoxy.

**[0024]** The term "(m-nC)" or "(m-nC) group" used alone or as a prefix, refers to any group having m to n carbon atoms.

**[0025]** “Cycloalkyl” means a hydrocarbon monocyclic or bicyclic ring containing carbon atoms. Examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl. Bicyclic rings may be fused or spiro attached; examples of bicyclic cycloalkyl groups include bicyclo[2.2.2]octane, bicyclo[2.1.1]hexane, bicyclo[1.1.1]pentane, spiro[2.4]heptane, bicyclo[4.1.0]heptane and bicyclo[2.2.1]heptane.

**[0026]** The term “halo” refers to fluoro, chloro, bromo and iodo.

**[0027]** The term “haloalkyl” is used herein to refer to an alkyl group respectively in which one or more hydrogen atoms have been replaced by halogen (e.g. fluorine) atoms. Examples of haloalkyl groups include fluoroalkyl groups such as –$CHF_2$, –$CH_2CF_3$, or perfluoroalkyl/alkoxy groups such as –$CF_3$, or –$CF_2CF_3$.

**[0028]** The term "heterocyclyl", "heterocyclic" or "heterocycle" means a non-aromatic saturated or partially saturated monocyclic, fused, bridged, or spiro bicyclic heterocyclic ring system(s). Monocyclic heterocyclic rings contain from about 3 to 12 (suitably from 3 to 7) ring atoms, with from 1 to 5 (suitably 1, 2 or 3) heteroatoms selected from nitrogen, oxygen or sulfur in the ring. Bicyclic heterocycles contain from 7 to 17 member atoms, suitably 7 to 12 member atoms, in the ring. Bicyclic heterocyclic(s) rings may be fused, spiro, or bridged ring systems. Conveniently, the heterocyclic group is a 4- to 10-membered heterocyclyl. Suitable 4- to 10-membered heterocyclyl groups comprise monocyclic and bicyclic heterocycles. Conveniently, the monocyclic heterocycles contain 4 to 6 ring atoms with 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur in the ring. Conveniently, the bicyclic heterocycles contain 8 to 10 ring atoms with 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur in the ring. Suitable bicyclic heterocyclyl groups comprise 8- to 10-membered spiro bicyclic heterocyclic ring systems (such as 2-azaspiro[4.5]decanyl, 2-azaspiro[4.4]nonanyl, 2,8-diazaspiro[4.5]decanyl, 8-oxa-2-azaspiro[4.5]decanyl, or 1,3-diazaspiro[4.5]decanyl). Examples of heterocyclic groups include cyclic ethers such as oxiranyl, oxetanyl, tetrahydrofuranyl, dioxanyl, and substituted cyclic ethers. Heterocycles containing nitrogen include, for example, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, tetrahydrotriazinyl, tetrahydropyrazolyl, 1,2-diazacyclohexanyl, and the like. Typical sulfur containing heterocycles include tetrahydrothienyl, dihydro-1,3-dithiol, tetrahydro-2*H*-thiopyran, and hexahydrothiepine. Other heterocycles include dihydro-oxathiolyl, dihydroisoxazolyl (such as 4,5-dihydroisoxazolyl), dihydropyridinyl (such as 1,2-dihydropyridinyl or 1,6-dihydropyridinyl), tetrahydro-oxazolyl, tetrahydro-oxadiazolyl, tetrahydro-dioxazolyl, tetrahydro-oxathiazolyl, hexahydrotriazinyl, tetrahydro-oxazinyl, morpholinyl, thiomorpholinyl, tetrahydropyrimidinyl, dioxolinyl, octahydrobenzofuranyl, octahydrobenzimidazolyl, and octahydrobenzothiazolyl. For heterocycles containing sulfur, the oxidized sulfur heterocycles containing SO or $SO_2$ groups are also included. Examples include the sulfoxide and sulfone forms of tetrahydrothienyl and thiomorpholinyl such as tetrahydrothiene 1,1-dioxide and thiomorpholinyl 1,1-dioxide. A suitable value for a heterocyclyl group which bears 1 or 2 oxo (=O) or thioxo (=S) substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl. Particular heterocyclyl groups are saturated monocyclic 3 to 7 membered heterocyclyls containing 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur, for example azetidinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, tetrahydrothienyl, tetrahydrothienyl 1,1-dioxide, thiomorpholinyl, thiomorpholinyl 1,1-dioxide, piperidinyl, homopiperidinyl, piperazinyl or homopiperazinyl. As the skilled person would appreciate, any heterocycle may be linked to another group *via* any suitable atom, such as *via* a carbon or nitrogen atom. Suitably, the term "heterocyclyl",

"heterocyclic" or "heterocycle" will refer to 4, 5, 6 or 7 membered monocyclic rings as defined above, unless specified otherwise.

**[0029]** The term "heteroaryl" or "heteroaromatic" means an aromatic mono-, bi-, or polycyclic ring incorporating one or more (for example 1-4, particularly 1, 2 or 3) heteroatoms selected from nitrogen, oxygen or sulfur. Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring, for example a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulfur and oxygen. Typically, the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general, the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five. Suitably, the term "heteroaryl" or "heteroaromatic" will refer to 5 or 6 membered monocyclic heteroaryl rings as defined above.

**[0030]** Non-limiting examples of heteroaryl include furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, isoindolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, purinyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl, pteridinyl, naphthyridinyl, carbazolyl, phenazinyl, benzisoquinolinyl, pyridopyrazinyl, thieno[2,3-*b*]furanyl, 2*H*-furo[3,2-*b*]-pyranyl, 5*H*-pyrido[2,3-*d*]-o-oxazinyl, 1*H*-pyrazolo[4,3-*d*]-oxazolyl, 4*H*-imidazo[4,5-*d*]thiazolyl, pyrazino[2,3-*d*]pyridazinyl, imidazo[2,1-*b*]thiazolyl, imidazo[1,2-*b*][1,2,4]triazinyl. "Heteroaryl" also covers partially aromatic bi- or polycyclic ring systems wherein at least one ring is an aromatic ring and one or more of the other ring(s) is a non-aromatic, saturated or partially saturated ring, provided at least one ring contains one or more heteroatoms selected from nitrogen, oxygen or sulfur. Examples of partially aromatic heteroaryl groups include for example, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 2-oxo-1,2,3,4-tetrahydroquinolinyl, dihydrobenzthienyl, dihydrobenzfuranyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,3]dioxolyl, 2,2-dioxo-1,3-dihydro-2-benzothienyl, 4,5,6,7-tetrahydrobenzofuranyl, indolinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, 1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazinyl, 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, 4,5,6,7-tetrahydrobenzo[*d*]isoxazolyl, 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyridinyl, 5,6-dihydro-8*H*-[1,2,4]triazolo[3,4-*c*][1,4]oxazinyl, 5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazolyl, 6,7-

dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazolyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyridinyl, 6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]-oxazinyl and 1,4,5,6-tetrahydrocyclopenta[*d*][1,2,3]-triazol-5-yl.

**[0031]** Non-limiting examples of five membered heteroaryl groups include but are not limited to pyrrolyl, furanyl, thienyl, imidazolyl, furazanyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl and tetrazolyl groups.

**[0032]** Non-limiting examples of six membered heteroaryl groups include but are not limited to pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl and triazinyl.

**[0033]** Particular non-limiting examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzofuranyl, benzothiophenyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, isobenzofuranyl, indolyl, isoindolyl, indolizinyl, indolinyl, isoindolinyl, purinyl (e.g., adeninyl, guaninyl), indazolyl, benzodioxolyl, pyrrolopyridine, and pyrazolopyridinyl groups.

**[0034]** Particular non-limiting examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinolinyl, isoquinolinyl, chromanyl, thiochromanyl, chromenyl, isochromenyl, chromanyl, isochromanyl, benzodioxanyl, quinolizinyl, benzoxazinyl, benzodiazinyl, pyridopyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl groups.

**[0035]** Particular non-limiting examples of bicyclic heteroaryl groups containing a five membered ring fused to a five membered ring include but are not limited to 6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazolyl and 1,4,5,6-tetrahydrocyclopenta[*d*][1,2,3]triazol-5-yl.

**[0036]** The term “aryl” means a cyclic or polycyclic aromatic ring having from 6 to 12 carbon atoms. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and the like. In this particular embodiment, an aryl is phenyl or naphthyl, especially phenyl.

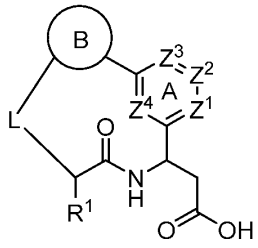
**[0037]** The term "optionally substituted" refers to either groups, structures, or molecules that are substituted and those that are not substituted.

**[0038]** Where optional substituents are chosen from “one or more” groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

**[0039]** The phrase “compound of the invention” means those compounds which are disclosed herein, both generically and specifically.

Compounds of the Invention

**[0040]** In a first aspect, the present invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof:



(I)

wherein:

A is an aromatic ring and $Z^1$, $Z^2$, $Z^3$ and $Z^4$ are independently N or $CR^2$;

B is aryl, 5- to 10-membered heteroaryl, $C_{3-10}$cycloalkyl, or 4- to 10-membered heterocyclyl; wherein B is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, cyano, hydroxyl, $NR^3R^4$, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-10}$cycloalkyl, and 4- to 10-membered heterocyclyl;

L is $C_{3-8}$alkylene, $C_{3-8}$alkenylene, or $C_{3-8}$alkynylene, wherein one, two or three methylene groups in L are optionally substituted with -O-, -S-, -C(O)-, or -N($R^5$)-; and wherein L is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, hydroxyl, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, and $NR^6R^7$;

$R^1$ is 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, aryl, $C_{3-10}$cycloalkyl, or -$NR^8C(O)R^9$; wherein:

i) each of 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, aryl, and $C_{3-10}$cycloalkyl is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, oxo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{1-4}$alkylene-OH, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$; and

ii) the 4- to 10-membered heterocyclyl group optionally contains one or two carbon-carbon double bonds, and is optionally fused to a 5- or 6-membered heteroaryl ring, or a phenyl ring;

$R^2$ at each occurrence is independently selected from H, halo, cyano, hydroxyl, $C_{1-5}$alkyl, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-6}$cycloalkyl and 4-6 membered heterocyclyl;

$R^3$ and $R^4$ are independently selected from H, $C_{1-5}$alkyl, $C_{1-5}$haloalkyl, and $C_{3-10}$cycloalkyl;

$R^5$, $R^6$ and $R^7$ are independently H or $C_{1-5}$alkyl;

$R^8$ is H, $C_{1-6}$alkyl, $C_{2-6}$haloalkyl, $C_{2-4}$alkylene-O-$C_{1-4}$alkyl; $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, or $C_{2-5}$alkylene-$NR^{12}R^{13}$;

$R^9$ is $C_{1-6}$alkyl, $C_{1-6}$alkoxy, $C_{1-6}$haloalkyl, $C_{1-6}$haloalkoxy, $C_{2-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, $NR^{14}R^{15}$ or $C_{1-5}$alkylene-$NR^{16}R^{17}$;

$R^{10}$ and $R^{11}$ are independently H, $C_{1-5}$alkyl, $C_{1-5}$haloalkyl or -$C_{1-4}$alkylene-O-$C_{1-4}$alkyl; or

$R^{10}$ and $R^{11}$, taken together with the nitrogen to which they are attached, form a 4- to 6-membered heterocyclyl ring optionally substituted with one to four groups independently selected from halo, $C_{1-5}$alkyl, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, and $C_{1-5}$haloalkoxy; and

$R^{12}$, $R^{13}$, $R^{14}$, $R^{15}$, $R^{16}$, and $R^{17}$ are independently H, $C_{1-5}$alkyl, or $C_{1-5}$haloalkyl; or

$R^{12}$ and $R^{13}$, $R^{14}$ and $R^{15}$, or $R^{16}$ and $R^{17}$, taken together with the nitrogen atoms to which they are attached, independently form a 4- to 6-membered heterocyclyl ring optionally substituted with one to four groups independently selected from halo and $C_{1-5}$alkyl.

**[0041]** Particular compounds of the invention include, for example, compounds of the formula I, or pharmaceutically acceptable salts thereof, wherein, unless otherwise stated, each of $Z^1$, $Z^2$, $Z^3$, $Z^4$, A, B, L, $R^1$, $R^2$, $R^{10}$, and $R^{11}$ has any of the meanings defined hereinbefore or in any of paragraphs (1) to (60) hereinafter. For the avoidance of doubt, the scope of the present invention encompasses compounds of formula I, or pharmaceutically acceptable salts thereof, wherein any of the substituent definitions defined herein may be combined with any of the other substituent definitions also defined herein:

(1) $Z^1$, $Z^2$, $Z^3$ and $Z^4$ are all $CR^2$;

(2) Two of $Z^1$, $Z^2$, $Z^3$ and $Z^4$ are N and the other two are $CR^2$;

(3) One of $Z^1$, $Z^2$, $Z^3$ and $Z^4$ is N and the other three are $CR^2$;

(4) $Z^2$ is N and $Z^1$, $Z^3$ and $Z^4$ are $CR^2$;

(5) $R^2$ at each occurrence is independently selected from H, halo, cyano, hydroxyl, $C_{1-5}$alkyl, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, and $C_{3-6}$cycloalkyl;

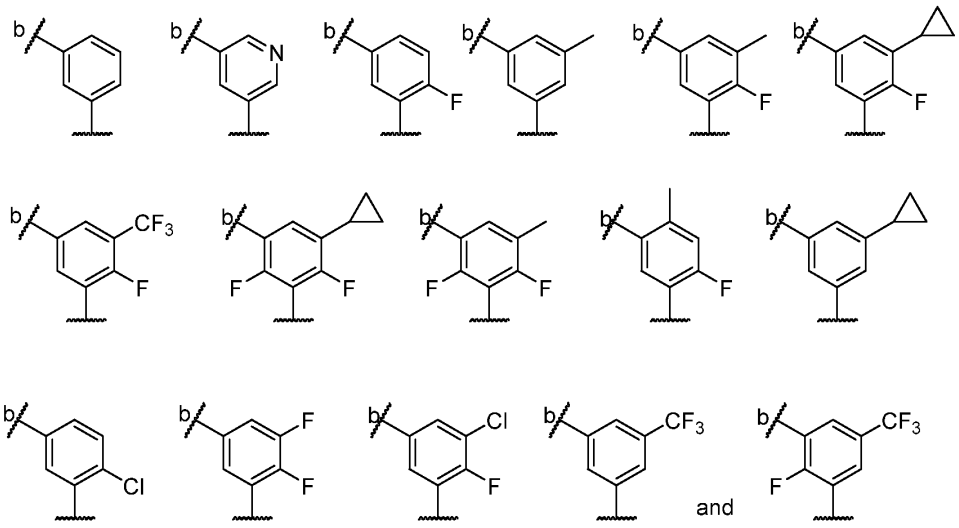
(6) $R^2$ at each occurrence is independently selected from H, halo, $C_{1-5}$alkyl, $C_{1-5}$haloalkyl, and $C_{3-6}$cycloalkyl;

(7) $R^2$ at each occurrence is independently selected from H, fluoro, chloro, methyl, ethyl, trifluoromethyl, and cyclopropyl;

(8) $R^2$ at each occurrence is independently selected from H, fluoro, methyl, trifluoromethyl, and cyclopropyl;

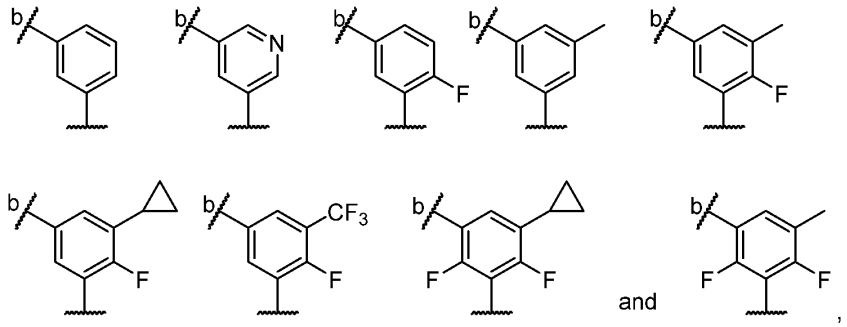
(9) $R^2$ at each occurrence is H;

(10) A is selected from:



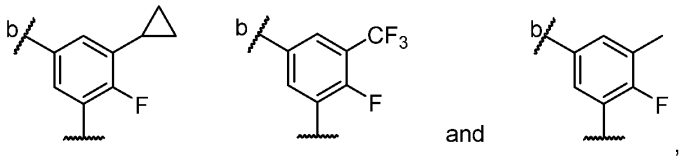

wherein 'b' is the point of attachment to the B ring;

(11) A is selected from:




wherein 'b' is the point of attachment to the B ring;

(12) A is selected from:




wherein 'b' is the point of attachment to the B ring;

(13) B is aryl, 5- to 6-membered heteroaryl, $C_{3-8}$cycloalkyl, or 4- to 8-membered heterocyclyl; wherein B is optionally substituted with one to five substituents independently selected

from $C_{1-5}$alkyl, halo, cyano, hydroxyl, $NR^3R^4$, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-10}$cycloalkyl, and 4- to 10-membered heterocyclyl;

(14) B is aryl, or 5- to 6-membered heteroaryl; wherein B is optionally substituted with one to four substituents independently selected from $C_{1-3}$alkyl, halo, cyano, hydroxyl, $NR^3R^4$, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-7}$cycloalkyl, and 4- to 10-membered heterocyclyl;

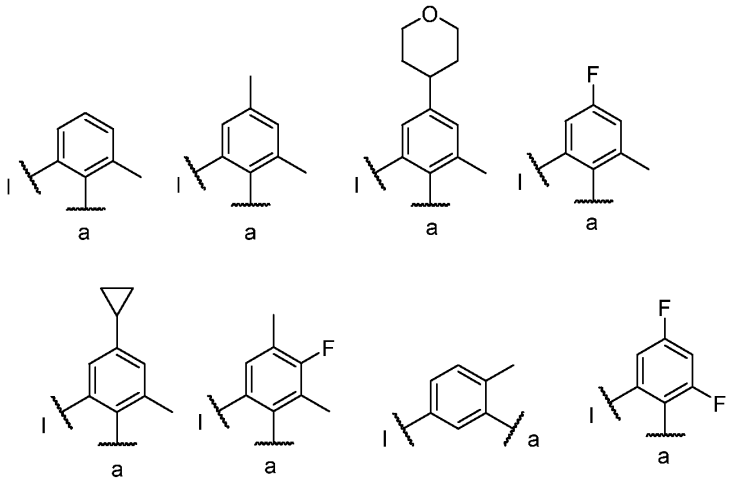
(15) B is aryl, optionally substituted with one to four substituents independently selected from $C_{1-3}$alkyl, halo, cyano, hydroxyl, $NR^3R^4$, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-7}$cycloalkyl, and 4- to 10-membered heterocyclyl;

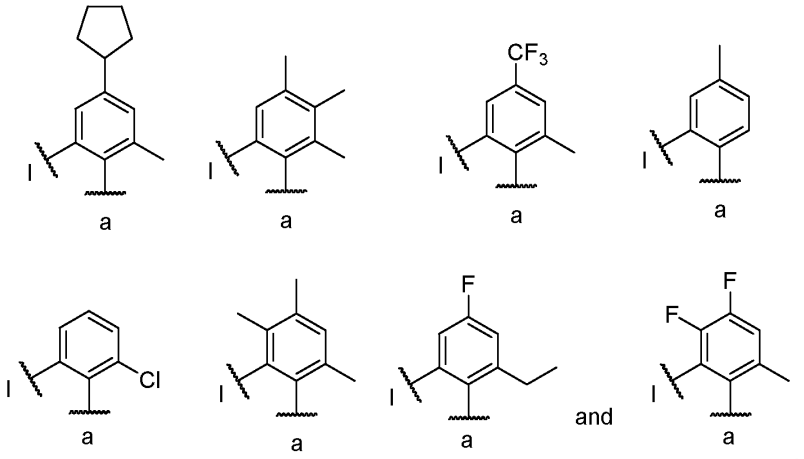
(16) B is phenyl, optionally substituted with one to four substituents independently selected from $C_{1-3}$alkyl, halo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{3-7}$cycloalkyl, and 4- to 10-membered heterocyclyl;

(17) B is phenyl, optionally substituted with one to three substituents independently selected from $C_{1-3}$alkyl, halo, $C_{3-7}$cycloalkyl, and 4- to 10-membered heterocyclyl;

(18) B is phenyl, optionally substituted with one to three substituents independently selected from methyl, fluoro, cyclopropyl, and 5- to 6-membered heterocyclyl;

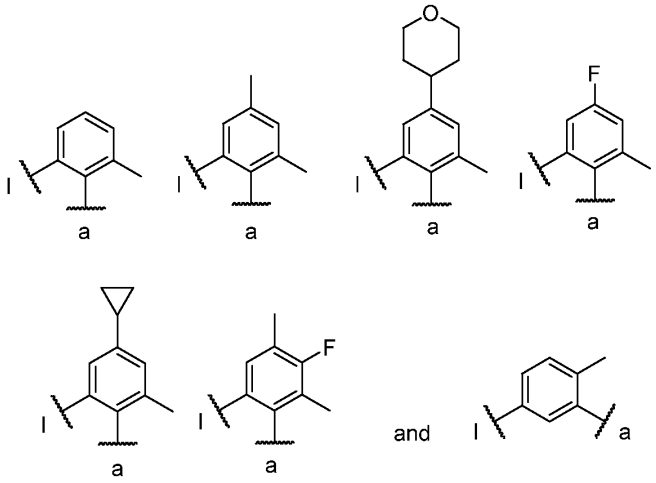
(19) B is selected from:





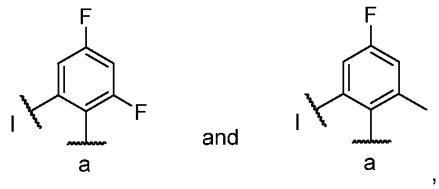

wherein 'a' is the point of attachment to the A ring and 'l' is the point of attachment to the linker L;

(20) B is selected from:




wherein 'a' is the point of attachment to the A ring and 'l' is the point of attachment to the linker L;

(21) B is selected from:




wherein 'a' is the point of attachment to the A ring and 'l' is the point of attachment to the linker L;

(22) L is $C_{3-8}$alkylene, or $C_{3-8}$alkenylene, wherein one, two or three methylene groups in L are optionally substituted with -O-, -S-, -C(O)-, or -N($R^5$)-; and wherein L is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, hydroxyl, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, and $NR^6R^7$;

(23) L is $C_{5-8}$alkylene, or $C_{5-8}$alkenylene, wherein one, two or three methylene groups in L are optionally substituted with -O-, -S-, -C(O)-, or -N($R^5$)-; and wherein L is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, hydroxyl, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, and $NR^6R^7$;

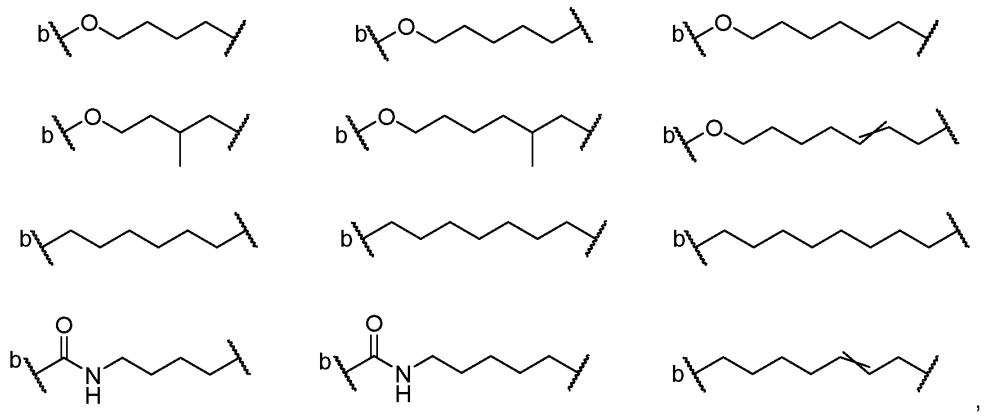
(24) L is $C_{5-8}$alkylene, or $C_{5-8}$alkenylene, wherein one, two or three methylene groups in L are optionally substituted with -O-, -C(O)-, or -N($R^5$)-; and wherein L is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, hydroxyl, $C_{1-5}$alkoxy, and $C_{1-5}$haloalkyl;

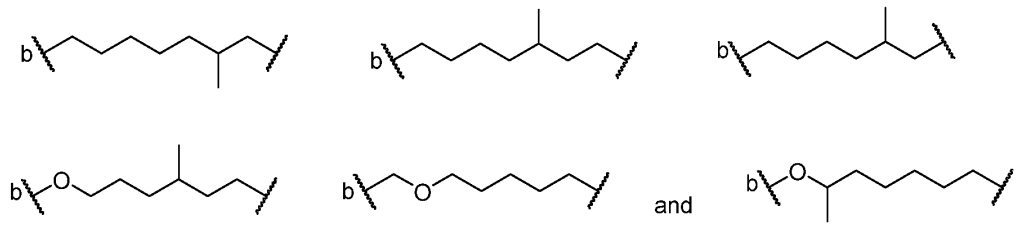
(25) L is $C_{5-8}$alkylene, or $C_{5-8}$alkenylene, wherein one or two methylene groups in L are optionally substituted with -O-, -C(O)-, or -N($R^5$)-; and wherein L is optionally substituted with one to three substituents independently selected from $C_{1-5}$alkyl, halo, hydroxyl, $C_{1-5}$alkoxy, and $C_{1-5}$haloalkyl;

(26) L is $C_{5-8}$alkylene, wherein one or two methylene groups in L are optionally substituted with -O-, -C(O)-, or -N($R^5$)-; and wherein L is optionally substituted with one to three independently selected $C_{1-5}$alkyl substituents;

(27) L is $C_{5-8}$alkylene, wherein one or two methylene groups in L are optionally substituted with -O-, -C(O)-, or -N($R^5$)-; and wherein L is optionally substituted with one to three methyl substituents;

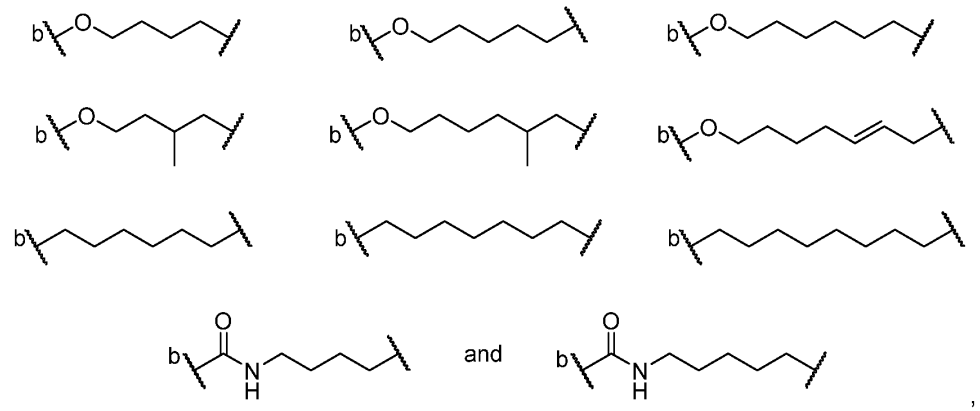
(28) L is selected from:





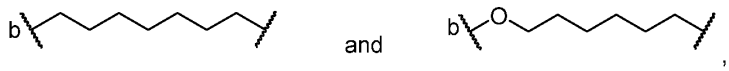
wherein 'b' is the point of attachment to the B ring;

(29) L is selected from:



wherein 'b' is the point of attachment to the B ring;

(30) L is selected from:



wherein 'b' is the point of attachment to the B ring;

(31) $R^1$ is 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, aryl, $C_{3-10}$cycloalkyl, or $-NR^8C(O)R^9$; wherein:

i) each of 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, aryl, and $C_{3-10}$cycloalkyl is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, oxo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$; and

ii) the 4- to 10-membered heterocyclyl group optionally contains one or two carbon-carbon double bonds, and is optionally fused to a 5- or 6-membered heteroaryl ring, or a phenyl ring;

(32) $R^1$ is 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or $-NR^8C(O)R^9$; wherein:

i) each of 4- to 10-membered heterocyclyl, and 5- to 10-membered heteroaryl is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, oxo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$; and

ii) the 4- to 10-membered heterocyclyl group optionally contains one or two carbon-carbon double bonds, and is optionally fused to a 5- or 6-membered heteroaryl ring, or a phenyl ring;

(33) $R^1$ is 4- to 10-membered heterocyclyl, or $-NR^8C(O)R^9$; wherein the 4- to 10-membered heterocyclyl:

i) is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, oxo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$; and

ii) optionally contains one or two carbon-carbon double bonds, and is optionally fused to a 5- or 6-membered heteroaryl ring, or a phenyl ring;

(34) $R^1$ is 5- to 6-membered heterocyclyl; optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, oxo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$; optionally containing one or two carbon-carbon double bonds; and optionally fused to a phenyl ring;

(35) $R^1$ is 5- to 6-membered heterocyclyl; optionally substituted with one to four substituents independently selected from $C_{1-5}$alkyl, halo, oxo, cyano, $C_{1-5}$haloalkyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$; optionally containing one or two carbon-carbon double bonds; and optionally fused to a phenyl ring;

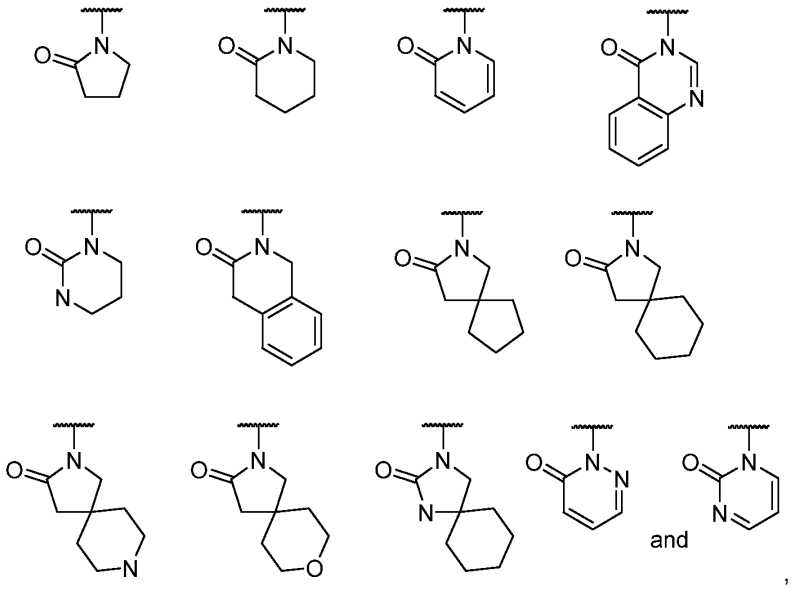
(36) $R^1$ is $-NR^8C(O)R^9$;

(37) $R^1$ is $-NR^8C(O)R^9$, and $R^8$ is H or $C_{1-6}$alkyl;

(38) $R^1$ is $-NR^8C(O)R^9$, and $R^9$ is $C_{1-6}$alkyl;

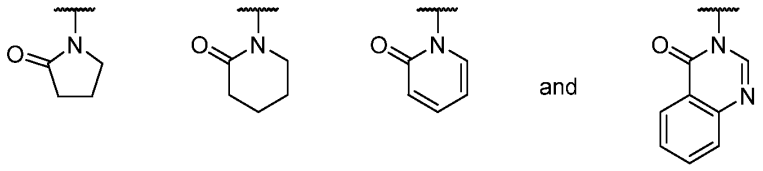
(39) $R^1$ is $-NR^8C(O)R^9$, $R^8$ is H or $C_{1-6}$alkyl, and $R^9$ is $C_{1-6}$alkyl;

(40) $R^1$ is selected from:



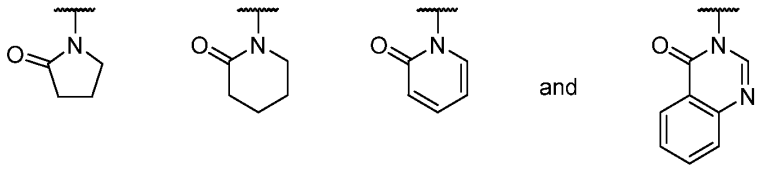
optionally substituted with one to three substituents independently selected from $C_{1-5}$alkyl, halo, oxo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{1-4}$alkylene-OH, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$;

(41) $R^1$ is selected from:



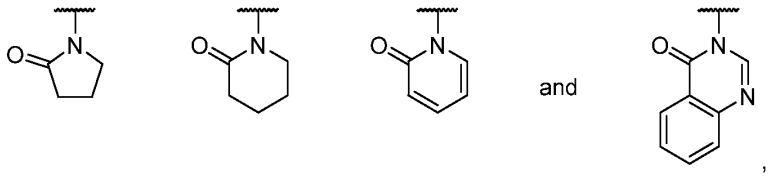
optionally substituted with one to three substituents independently selected from $C_{1-5}$alkyl, halo, oxo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$;

(42) $R^1$ is selected from:



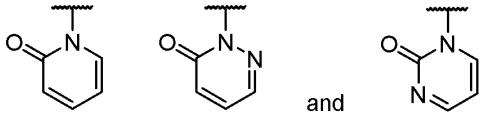
optionally substituted with one to three substituents independently selected from $C_{1-5}$alkyl, halo, $C_{1-5}$haloalkyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$;

(43) $R^1$ is selected from:



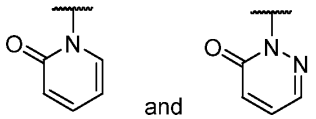
optionally substituted with one to three substituents independently selected from methyl, fluoro, trifluoromethyl, and $C_{2-3}$alkylene-$NR^{10}R^{11}$;

(44) $R^1$ is selected from:



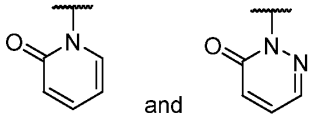
optionally substituted with one to three substituents independently selected from $C_{1-5}$alkyl, halo, oxo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{1-4}$alkylene-OH, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$;

(45) $R^1$ is selected from:



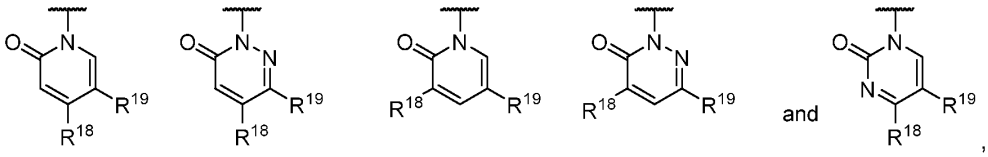
optionally substituted with one to three substituents independently selected from $C_{1-5}$alkyl, halo, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-4}$alkylene-OH, $C_{3-6}$cycloalkyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$;

(46) $R^1$ is selected from:



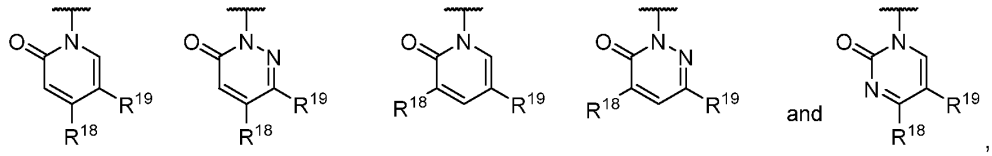
optionally substituted with one to three substituents independently selected from $C_{1-3}$alkyl, fluoro, chloro, methoxy, $C_{1-2}$haloalkyl, $C_{1-4}$alkylene-OH, $C_{3-4}$cycloalkyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$;

(47) $R^1$ is selected from:



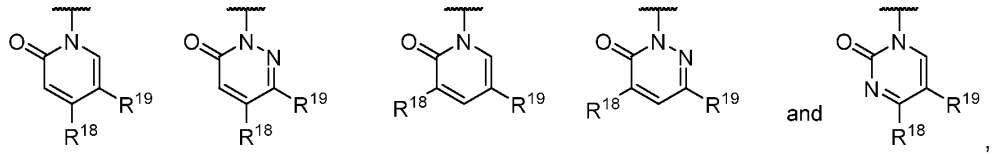
wherein $R^{18}$ is selected from hydrogen, $C_{1-5}$alkyl, halo, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, and $C_{3-6}$cycloalkyl; and $R^{19}$ is selected from hydrogen, halo, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{1-4}$alkylene-OH, and $C_{1-4}$alkylene-$NR^{10}R^{11}$;

(48) $R^1$ is selected from:



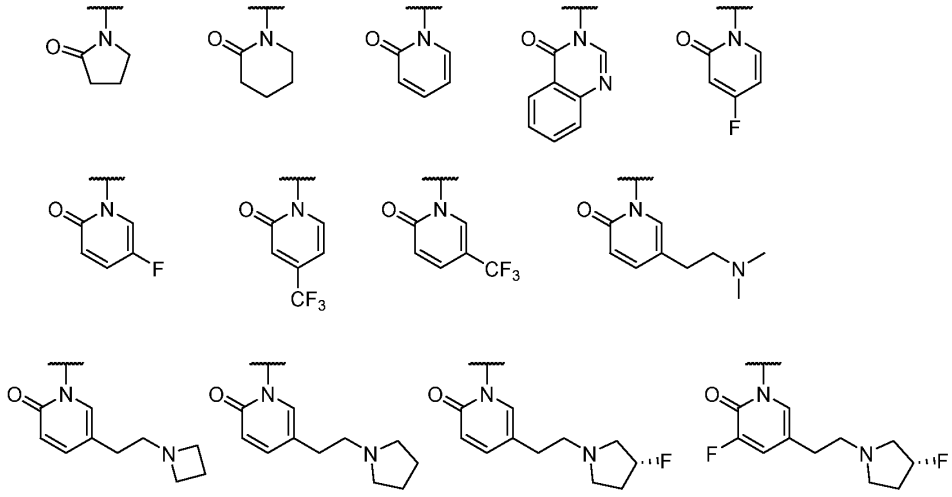
wherein $R^{18}$ is selected from hydrogen, methyl, halo, methoxy, $C_{1-2}$haloalkyl, and $C_{3-4}$cycloalkyl; and $R^{19}$ is selected from hydrogen, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{1-4}$alkylene-H, and $C_{1-4}$alkylene-$NR^{10}R^{11}$;

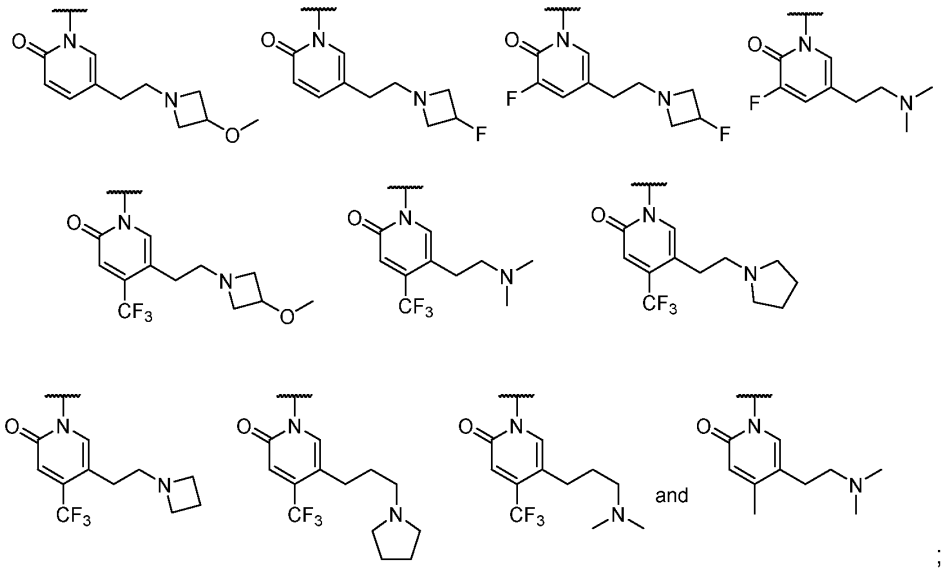
(49) $R^1$ is selected from:



wherein $R^{18}$ is selected from hydrogen, methyl, fluoro, trifluoromethyl, methoxy, and cyclopropyl; and $R^{19}$ is selected from hydrogen, and $C_{2-3}$alkylene-$NR^{10}R^{11}$;

(50) $R^1$ is selected from:






;

(51) $R^{10}$ and $R^{11}$ are independently H or $C_{1-5}$alkyl;

(52) $R^{10}$ and $R^{11}$ are independently H or methyl;

(53) $R^{10}$ and $R^{11}$ are both $C_{1-5}$alkyl;

(54) $R^{10}$ and $R^{11}$ are both methyl;

(55) $R^{10}$ and $R^{11}$, taken together with the nitrogen to which they are attached, form a 4- to 6-membered heterocyclyl ring optionally substituted with one to four groups independently selected from halo, $C_{1-5}$alkyl, $C_{1-5}$alkoxy, and $C_{1-5}$haloalkyl;

(56) $R^{10}$ and $R^{11}$, taken together with the nitrogen to which they are attached, form a 4- to 6-membered heterocyclyl ring optionally substituted with one to four groups independently selected from halo and $C_{1-5}$alkoxy;

(57) $R^{10}$ and $R^{11}$, taken together with the nitrogen to which they are attached, form a 4- to 5-membered heterocyclyl ring optionally substituted with one to three groups independently selected from halo and $C_{1-5}$alkoxy;

(58) $R^{10}$ and $R^{11}$, taken together with the nitrogen to which they are attached, form a 4- to 5-membered heterocyclyl ring optionally substituted with one or two groups independently selected from fluoro and methoxy;

(59) $R^{10}$ and $R^{11}$, taken together with the nitrogen to which they are attached, form an azetidinyl, pyrrolidinyl, or morpholinyl ring, each being optionally substituted with one or two groups independently selected from fluoro and methoxy;

(60) $R^{10}$ and $R^{11}$, taken together with the nitrogen to which they are attached, form an azetidinyl ring optionally substituted with one or two groups independently selected from fluoro and methoxy.

**[0042]** Suitably, $Z^1$, $Z^2$, $Z^3$ and $Z^4$ are as defined in any one of paragraphs (1) to (4) above. Preferably, $Z^1$, $Z^2$, $Z^3$ and $Z^4$ are as defined in paragraph (1) or paragraph (4) above.

**[0043]** Suitably, $R^2$ is as defined in any one of paragraphs (5) to (9) above.

**[0044]** Suitably, A is as defined in any one of paragraphs (10) to (12) above. Preferably, A is as defined in paragraph (12) above.

**[0045]** Suitably, B is as defined in any one of paragraphs (13) to (21) above. Preferably, B is as defined in paragraph (20) or paragraph (21) above.

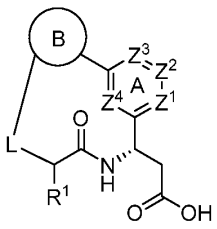
**[0046]** Suitably, L is as defined in any one of paragraphs (22) to (30) above. In an embodiment, L is as defined in in any one of paragraphs (27) to (30) above. In an embodiment, L is as defined in paragraph (30) above.

**[0047]** Suitably, $R^1$ is as defined in any one of paragraphs (31) to (50) above. In an embodiment, $R^1$ is as defined in in any one of paragraphs (44) to (49) above. In an embodiment, $R^1$ is as defined in paragraph (49) above.

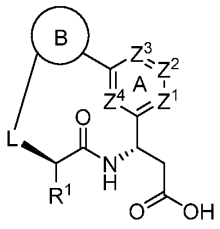
**[0048]** Suitably, $R^{10}$ and $R^{11}$ are as defined in any one of paragraphs (51) to (60) above. Preferably, $R^{10}$ and $R^{11}$ are as defined in paragraph (59) or paragraph (60) above.

**[0049]** Conveniently, the compound of Formula (I) has one of the sub-structural formulae (IA) to (IF) described hereinafter.

**[0050]** In an embodiment there is provided a compound of formula IA or IB, or a pharmaceutically acceptable salt thereof, wherein $Z^1$, $Z^2$, $Z^3$, $Z^4$, B, L and $R^1$ are as defined herein:

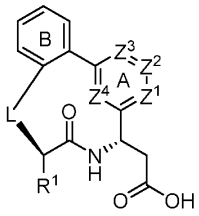



(IA)

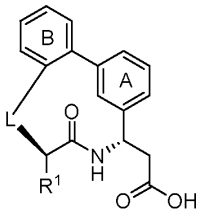



(IB)

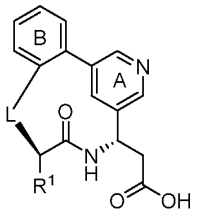
**[0051]** In an embodiment there is provided a compound according to any one of formulae IC to IL, or a pharmaceutically acceptable salt thereof, wherein $Z^1$, $Z^2$, $Z^3$, $Z^4$, L and $R^1$ are as defined herein:



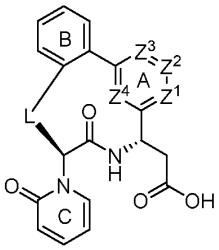
(IC)



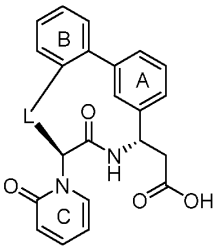
(ID)



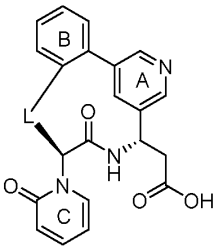
(IE)



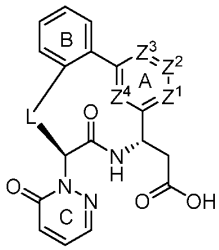
(IF)



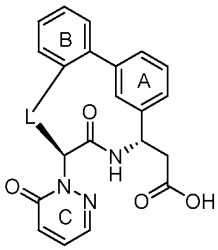
(IG)



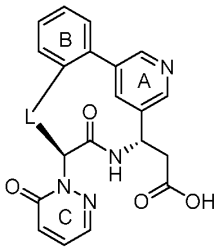
(IH)



(IJ)



(IK)



(IL)

,

wherein the A ring in formulae ID, IE, IG, IH, IK, and IL is optionally substituted with one to three groups independently selected from halo, cyano, hydroxyl, $C_{1-5}$alkyl, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-6}$cycloalkyl and 4-6 membered heterocyclyl; the B ring in formulae IC to IL is optionally substituted with one to four groups independently selected from $C_{1-5}$alkyl, halo, cyano, hydroxyl, $NR^3R^4$, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-10}$cycloalkyl, and 4- to 10-membered heterocyclyl; and the C ring in formulae IF, IG, IH, IJ, IK, and IL is optionally substituted with one to three groups independently selected from $C_{1-5}$alkyl, halo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$.

**[0052]** In a further group of compounds, the compounds have the structural formulae IC to IL above, wherein L is as defined in any one of paragraphs (27) to (30) above; $R^1$ in formulae IC, ID and IE is as defined in any one of paragraphs (44) to (46); the A ring in formulae ID, IE, IG, IH, IK, and IL is optionally substituted with one to three groups independently selected from halo, $C_{1-5}$alkyl, $C_{1-5}$haloalkyl, and $C_{3-6}$cycloalkyl; the B ring in formulae IC to IL is optionally

substituted with one to three groups independently selected from $C_{1-3}$alkyl, halo, $C_{3-7}$cycloalkyl, and 4- to 10-membered heterocyclyl; and the C ring in formulae IF, IG, IH, IJ, IK, and IL is optionally substituted with one to three groups independently selected from $C_{1-5}$alkyl, halo, $C_{1-5}$haloalkyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$.

**[0053]** In a further group of compounds, the compounds have the structural formulae IC to IL above, wherein L is as defined in paragraph (30) above; $R^1$ in formulae IC, ID and IE is as defined in paragraph (46) above; the A ring in formulae ID, IE, IG, IH, IK, and IL is optionally substituted with one to three groups independently selected from fluoro, methyl, trifluoromethyl, and cyclopropyl; the B ring in formulae IC to IL is optionally substituted with one to three groups independently selected from methyl, fluoro, cyclopropyl, and 5- to 6-membered heterocyclyl; and the C ring in formulae IF, IG, IH, IJ, IK, and IL is optionally substituted with one to three groups independently selected from methyl, fluoro, trifluoromethyl, and $C_{2-3}$alkylene-$NR^{10}R^{11}$.

**[0054]** In an embodiment, the compound according to formula I is selected from one of the following compounds, or a pharmaceutically acceptable salt thereof:

2-((9*S*,12*S*)-9-Acetamido-$2^6$-methyl-10-oxo-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid;
2-((8*S*,11*S*)-8-Acetamido-$2^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid;
2-((10*S*,13*S*)-10-Acetamido-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-Acetamido-$2^6$,8-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-acetamido-$2^6$-methyl-11-oxo-3-oxa-12-aza-1,2(1,3)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((8*S*,11*S*)-8-Acetamido-$2^6$,6-dimethyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid;
2-((10*S*,13*S*)-$2^6$-Methyl-10-(*N*-methylacetamido)-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6*S*)-$1^6$-Methyl-6-(*N*-methylacetamido)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((10*S*,13*S*)-$2^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-$2^6$-Methyl-11-oxo-10-(2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-$2^6$-Methyl-11-oxo-10-(2-oxopiperidin-1-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((9*S*,12*S*)-$2^6$-Methyl-10-oxo-9-(2-oxopiperidin-1-yl)-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid;
2-((10*S*,13*S*)-$2^6$-Methyl-11-oxo-10-(2-oxopyrrolidin-1-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((8*S*,11*S*)-2$^6$-Methyl-9-oxo-8-(2-oxopyridin-1(2*H*)-yl)-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid;
2-((10*S*,13*S*)-2$^4$-fluoro-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-Fluoro-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxopiperidin-1-yl)-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-2$^4$-Fluoro-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(4-Fluoro-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxo-5-(trifluoromethyl)pyridin-1(2H)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-1$^4$-Fluoro-1$^5$,2$^6$-dimethyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((8*S*,11*S*)-8-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid;
2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-2$^4$-(tetrahydro-2*H*-pyran-4-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6*S*)-6-Acetamido-1$^6$-methyl-5,12-dioxo-4,11-diaza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-Acetamido-1$^6$-methyl-5,13-dioxo-4,12-diaza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((11*S*,14*S*,*E*)-11-acetamido-2$^6$-methyl-12-oxo-3-oxa-13-aza-1(1,3),2(1,2)-dibenzenacyclotetradecaphan-8-en-14-yl)acetic acid;
2-((11*S*,14*S*)-11-Acetamido-2$^6$-methyl-12-oxo-3-oxa-13-aza-1(1,3),2(1,2)-dibenzenacyclotetradecaphane-14-yl)acetic acid;
2-((10*S*,13*S*)-2$^4$-Fluoro-2$^6$-methyl-10-(*N*-methylacetamido)-11-oxo-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-2$^4$-Fluoro-2$^6$-methyl-10-(*N*-methylacetamido)-11-oxo-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(4-oxoquinazolin-3(4*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(3-Fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-((*R*)-3-Fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(3-Methoxyazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(Azetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-$1^4$,$2^4$-Difluoro-10-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-$1^4$-Fluoro-10-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-$1^4$,$2^4$-Difluoro-10-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-$1^4$-fluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-$1^4$,$2^4$-Difluoro-10-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid
2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^2$,$1^4$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-$1^4$-fluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-24-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-$1^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((8*S*,11*S*)-8-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-$2^4$-fluoro-$2^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$-cyclopropyl-$1^2$,$1^4$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-$1^4$-fluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-10-(2-oxo-5-(3-(pyrrolidin-1-yl)propyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^5$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^2$,$1^4$-difluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^2$,$1^4$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotetradecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;
2-((10*S*,13*S*)-$1^5$-Cyclopropyl-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-$1^5$-Cyclopropyl-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-$1^5$-Cyclopropyl-10-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-1$^4$,2$^4$-Difluoro-2$^6$-methyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-2$^4$-Cyclopentyl-1$^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(3-(diethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-1$^4$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-1$^4$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((10*S*,13*S*)-1$^5$,2$^4$-Dicyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((9*S*,12*S*)-1$^5$,2$^4$-Dicyclopropyl-9-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-10-oxo-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid;
2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^5$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((9*S*,12*S*)-1$^5$-Cyclopropyl-9-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^5$,2$^6$-trimethyl-10-oxo-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^6$,2$^4$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;
2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-11-oxo-2$^4$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((9*S*,12*S*)-1$^5$-Cyclopropyl-9-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-10-oxo-2$^4$-(trifluoromethyl)-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-1$^4$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-1$^4$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$,2$^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$,2$^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-2$^4$-fluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^5$-cyclopropyl-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6S)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-2$^4$-fluoro-6-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((10*S*,13*S*)-1$^5$-Cyclopropyl-1$^4$-fluoro-10-(4-methoxy-2-oxopyridin-1(2*H*)-yl)-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(3-(3-fluoroazetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$,2$^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$,2$^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;
2-((10*S*,13*S*)-1$^5$-cyclopropyl-1$^4$-fluoro-10-(4-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-6-(4-methyl-2-oxopyridin-1(2*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^4$-Chloro-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(4-cyclopropyl-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(4-cyclopropyl-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$,2$^4$-trifluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-2$^4$-fluoro-6-(5-(3-(3-fluoroazetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(3-(Azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^2$,$2^4$-trifluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$1^6$-Chloro-$2^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(3-(Azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$,$2^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(4-(Difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$,$2^5$-trifluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$2^5$-Chloro-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((10*S*,13*S*)-$1^4$,$2^4$-Difluoro-$1^5$,$2^6$-dimethyl-11-oxo-10-(3-oxo-2-azaspiro[4.5]decan-2-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^3$,2$^4$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$,2$^4$-trifluoro-2$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^2$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^3$,2$^4$-trifluoro-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,8-dimethyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,8-dimethyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((10*S*,13*S*)-1$^4$,2$^4$-Difluoro-1$^5$,2$^6$-dimethyl-10-(3-methyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(3-(Azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$,2$^4$,2$^5$-tetrafluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$,2$^4$,2$^5$-tetrafluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-$1^6$-methyl-5-oxo-6-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-$1^6$-methyl-5-oxo-6-(3-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-$1^6$,$2^5$-dimethyl-5-oxo-6-(3-oxo-2-azaspiro[4.5]decan-2-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,9-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$-trifluoro-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$1^4$,$2^4$,$2^5$-Trifluoro-$1^6$-methyl-5-oxo-6-(3-oxo-2-azaspiro[4.5]decan-2-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((10*S*,13*S*)-10-(4,4-Dimethyl-2-oxopyrrolidin-1-yl)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-$1^6$-methyl-5-oxo-6-(3-oxo-2-azaspiro[4.4]nonan-2-yl)-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$2^5$-Cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-6-(3-oxo-2,8-diazaspiro[4.5]decan-2-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$2^5$-Cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-6-(8-methyl-3-oxo-2,8-diazaspiro[4.5]decan-2-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-6-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-Bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$,$2^5$-trifluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-$1^6$-methyl-5-oxo-6-(3-oxo-8-oxa-2-azaspiro[4.5]decan-2-yl)-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-ethyl-$1^4$,$2^4$-difluoro-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$-trifluoro-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$1^4$,$2^4$,$2^5$-Trifluoro-$1^6$-methyl-6-(1-methyl-2-oxo-1,3-diazaspiro[4.5]decan-3-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-6-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-12-oxa-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-2$^6$,7-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-2$^6$,4-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;
2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-1$^6$-methyl-6-(5-(2-morpholinoethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(3-(3-(dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(3-(3-(Azetidin-1-yl)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(3-hydroxypropyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-1$^4$,1$^6$,2$^4$-Trifluoro-6-(5-(2-morpholinoethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(3-(2-(Dimethylamino)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,1$^6$,2$^4$-trifluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$,2$^5$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^3$,1$^4$,2$^4$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(3-(2-(dimethylamino)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,1$^6$,2$^4$-trifluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyrimidin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;
2-((3*S*,6*S*)-6-(5-(2-(3-Methoxyazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid; and
2-((3*S*,6*S*)-6-(5-(2-(3-Fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid.

**[0055]** The various functional groups and substituents making up the compounds of the present invention are typically chosen such that the molecular weight of the compound does not exceed 1000. More usually, the molecular weight of the compound will be less than 800, for example less than 750, or less than 700.

**[0056]** Suitable or preferred features of any compounds of the present invention may also be suitable features of any other aspect.

**[0057]** A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulfuric, phosphoric, trifluoroacetic, formic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

**[0058]** Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”. Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric centre, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric centre and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a

mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

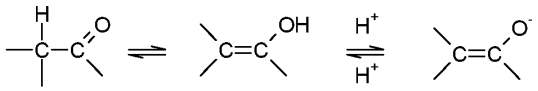
**[0059]** The compounds of this invention typically possess one or more asymmetric centres; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers, diastereoisomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 2001), for example by synthesis from optically active starting materials or by resolution of a racemic form. Some of the compounds of the invention may have geometric isomeric centres (E- and Z- isomers). It is to be understood that the present invention encompasses all optical, diastereoisomers and geometric isomers and mixtures thereof that possess $\alpha4\beta7$ inhibition activity.

**[0060]** The present invention also encompasses compounds of the invention as defined herein which comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including $^{1}H$, $^{2}H$ (D) and $^{3}H$ (T); C may be in any isotopic form including $^{12}C$, $^{13}C$, and $^{14}C$; and O may be in any isotopic form, including $^{16}O$ and $^{18}O$; and the like. In an embodiment, present invention also encompasses deuterated analogues of the compounds of the invention defined by formula I.

**[0061]** It is also to be understood that certain compounds of the invention may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms that possess $\alpha4\beta7$ inhibition activity.

**[0062]** It is also to be understood that certain compounds of the invention may exhibit polymorphism, and that the invention encompasses all such forms that possess $\alpha4\beta7$ inhibition activity.

**[0063]** Compounds of the invention may exist in a number of different tautomeric forms and references to compounds of the invention include all such forms. For the avoidance of doubt, where a compound can exist in one of several tautomeric forms, and only one is specifically described or shown, all others are nevertheless embraced by compounds of the invention. Examples of tautomeric forms include keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol and nitro/aci-nitro.




**[0064]** Compounds of the invention containing an amine function may also form *N*-oxides. A reference herein to a compound of the formula I that contains an amine function also includes the *N*-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an *N*-oxide. Particular examples of *N*-oxides are the *N*-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle. *N*-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, *N*-oxides can be made by the procedure of L. W. Deady (*Syn. Comm.* 1977, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.

**[0065]** The compounds of the invention may be administered in the form of a pro-drug which is broken down in the human or animal body to release a compound of the invention. A pro-drug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the invention. A pro-drug can be formed when the compound of the invention contains a suitable group or substituent to which a property-modifying group can be attached. Examples of pro-drugs include *in vivo* cleavable ester derivatives that may be formed at a carboxy group or a hydroxy group in a compound of the invention and *in-vivo* cleavable amide derivatives that may be formed at a carboxy group or an amino group in a compound of the invention.

**[0066]** Accordingly, the present invention includes those compounds of the formula I as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a pro-drug thereof. Accordingly, the present invention includes those compounds of the formula I that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of the formula I may be a synthetically-produced compound or a metabolically-produced compound.

**[0067]** A suitable pharmaceutically acceptable pro-drug of a compound of the formula I is one that is based on reasonable medical judgement as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity.

**[0068]** Various forms of pro-drug have been described, for example in the following documents:

a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al*. (Academic Press, 1985);

b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985);

c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, *et al*., Journal of Pharmaceutical Sciences, 77, 285 (1988);

f) N. Kakeya, *et al*., Chem. Pharm. Bull., 32, 692 (1984);

g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; and

h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

**[0069]** A suitable pharmaceutically acceptable pro-drug of a compound of the formula I that possesses a carboxy group is, for example, an *in vivo* cleavable ester thereof. An *in vivo* cleavable ester of a compound of the formula I containing a carboxy group is, for example, a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid. Suitable pharmaceutically acceptable esters for carboxy include $C_{1-6}$alkyl esters such as methyl, ethyl and *tert*-butyl, $C_{1-6}$alkoxymethyl esters such as methoxymethyl esters, $C_{1-6}$alkanoyloxymethyl esters such as pivaloyloxymethyl esters, 3-phthalidyl esters, $C_{3-8}$cycloalkylcarbonyloxy- $C_{1-6}$alkyl esters such as cyclopentylcarbonyloxymethyl and 1-cyclohexylcarbonyloxyethyl esters, 2-oxo-1,3-dioxolenylmethyl esters such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl esters and $C_{1-6}$alkoxycarbonyloxy-$C_{1-6}$alkyl esters such as methoxycarbonyloxymethyl and 1-methoxycarbonyloxyethyl esters.

**[0070]** A suitable pharmaceutically acceptable pro-drug of a compound of the formula I that possesses a hydroxy group is, for example, an *in vivo* cleavable ester or ether thereof. An *in vivo* cleavable ester or ether of a compound of the formula I containing a hydroxy group is, for example, a pharmaceutically acceptable ester or ether which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically acceptable ester forming groups for a hydroxy group include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically acceptable ester forming groups for a hydroxy group include $C_{1-10}$alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, $C_{1-10}$alkoxycarbonyl groups such as ethoxycarbonyl, *N*,*N*-$(C_{1-6})_2$carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include

aminomethyl, *N*-alkylaminomethyl, *N*,*N*-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-($C_{1-4}$alkyl)piperazin-1-ylmethyl. Suitable pharmaceutically acceptable ether forming groups for a hydroxy group include α-acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

**[0071]** A suitable pharmaceutically acceptable pro-drug of a compound of the formula I that possesses a carboxy group is, for example, an *in vivo* cleavable amide thereof, for example an amide formed with an amine such as ammonia, a $C_{1-4}$alkylamine such as methylamine, a $(C_{1-4}alkyl)_2$ amine such as dimethylamine, *N*-ethyl-*N*-methylamine or diethylamine, a $C_{1-4}$alkoxy- $C_{2-4}$alkylamine such as 2-methoxyethylamine, a phenyl-$C_{1-4}$alkylamine such as benzylamine and amino acids such as glycine or an ester thereof.

**[0072]** A suitable pharmaceutically acceptable pro-drug of a compound of the formula I that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically acceptable amides from an amino group include, for example an amide formed with $C_{1-10}$alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, *N*-alkylaminomethyl, *N*,*N*-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-($C_{1-4}$alkyl)piperazin-1-ylmethyl.

**[0073]** The *in vivo* effects of a compound of the formula I may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of the formula I. As stated hereinbefore, the *in vivo* effects of a compound of the formula I may also be exerted by way of metabolism of a precursor compound (a pro-drug).

**[0074]** It shall also be appreciated that compounds of the formula I may also be covalently linked (at any suitable position) to other groups such as, for example, solubilising moieties (for example, PEG polymers), moieties that enable them to be bound to a solid support (such as, for example, biotin-containing moieties), and targeting ligands (such as antibodies or antibody fragments).

Synthesis

**[0075]** The compounds of the disclosure may be prepared using methods disclosed herein and routine modifications thereof which will be apparent given the disclosure herein and methods well known in the art. Conventional and well-known synthetic methods may be used in addition to the teachings herein. The synthesis of typical compounds of Formula (I), e.g., compounds having structures described by Formula (I), or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, or deuterated analogue thereof, may be accomplished as described in the following examples.

**[0076]** In the description of the synthetic methods described below and in the referenced synthetic methods that are used to prepare the starting materials, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be selected by a person skilled in the art.

**[0077]** It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reaction conditions utilised.

**[0078]** Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively, necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

**[0079]** It will be appreciated that during the synthesis of the compounds of the invention in the processes defined below, or during the synthesis of certain starting materials, it may be desirable to protect certain substituent groups to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed.

**[0080]** For examples of protecting groups see one of the many general texts on the subject, for example, "Protecting groups in Organic Synthesis (3rd Ed), John Wiley & Sons, NY (1999)", T. Greene & P. Wuts. Protecting groups may be removed by any convenient method described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with the minimum disturbance of groups elsewhere in the molecule.

**[0081]** Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

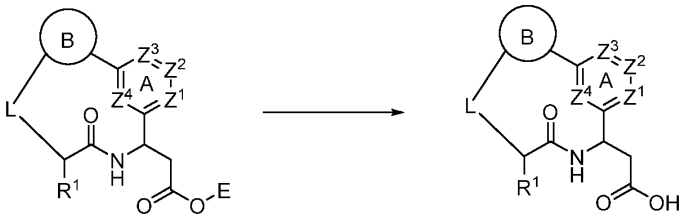
**[0082]** By way of example, a suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed by, for example, hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively, an acyl group such as a *tert*-butoxycarbonyl group may be removed, for

example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example $BF_3.OEt_2$. A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

**[0083]** The person skilled in the art will recognise that the compounds of the invention may be prepared, in known manner, in a variety of ways. Compounds of formula I can be prepared by the methods given below, by the methods given in the experimental or by analogous methods. The routes described are merely illustrative of some of the methods that can be employed for the synthesis of compounds of formula I and the person skilled in the art will appreciate that the order of the reaction steps is not limited to those described. It will also be appreciated that the assignment of nucleophile and electrophile is not limited to that described herein and in some cases it may be appropriate for the assignment to be reversed. Different approaches to synthetic chemistry strategy are described in "Organic Synthesis: The Disconnection Approach", 2nd edition, S. Warren and P. Wyatt (2008).

General Methods

**[0084]** Compounds of Formula (I) may be prepared by a process involving first deprotection, i.e. cleavage of an ester group, followed optionally by conversion to a salt, of a compound of formula (A1) where E is defined as $C_{1\text{-}6}$alkyl, for example tert-butyl or methyl, and all other variables are defined according to the scope of the present invention.

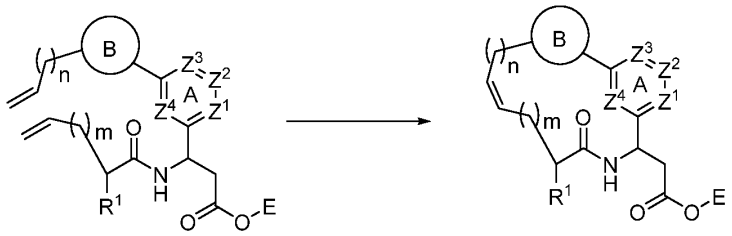



(A1) (I)

**[0085]** The deprotection of compounds of formula (A1), where E is tert-butyl, may be accomplished by acid hydrolysis using for example hydrochloric, sulfuric or trifluoroacetic acid, in a suitable solvent, such as dichloromethane, tetrahydrofuran or 1,4-dioxane. Where E is methyl, deprotection may be accomplished by base hydrolysis using for example lithium or sodium hydroxide in the presence of water and a suitable solvent such as methanol, ethanol, tetrahydrofuran or 1,4-dioxane.

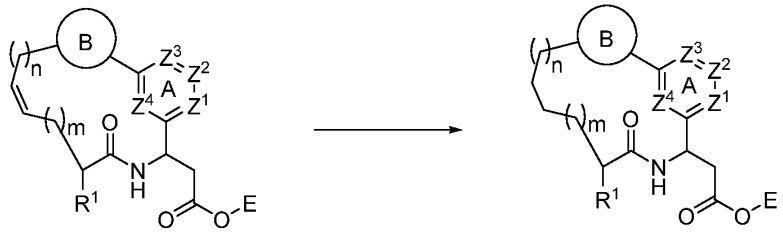
**[0086]** After the cleavage of the ester group, the resulting product may be converted to the required salt by methods well known to those skilled in the art.

**[0087]** Compounds of formula (A1), in which L is a -$C_{3-8}$alkenylene- group, where n and m are zero to six (provided n and m combined are one to six) and one, two or three methylene groups in the -$C_{3-8}$alkenylene- group are optionally substituted with -O-, -S-, -C(O)- or -N($R^5$)-, which are compounds of formula (A2), may be prepared from intermediates of formula (A3), via an olefin metathesis reaction in the presence of a suitable metal catalyst such as the ruthenium based catalysts reported by Robert H. Grubbs and Amir H. Hoveyda (DOI: 10.1021/ja952676d. DOI: 10.1021/ja983222u, DOI: 10.1021/ol990909q and DOI: 10.1021/ja001179g). The metathesis reaction may be conducted in a suitable solvent, such as tetrahydrofuran, 1,4-dioxane, dichloromethane, 1,2-dichloroethane or toluene, at an elevated temperature under nitrogen atmosphere.



(A3) (A2)

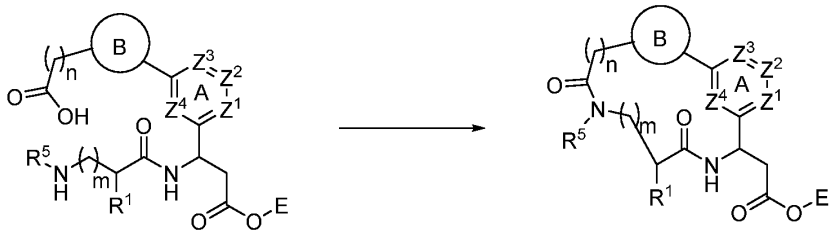
**[0088]** Compounds of formula (A1) in which L is -$C_{3-8}$alkylene-, which are compounds of formula (A4), may be prepared from compounds of formula (A2), by reduction of the double bond. The reduction may be accomplished by catalytic hydrogenation with hydrogen in the presence of a noble metal catalyst such as Pt, Pd, Rh, Ru or Raney nickel. The hydrogenation reaction is conducted in a solvent such as methanol, ethanol, tetrahydrofuran or mixtures thereof.



(A2) (A4)

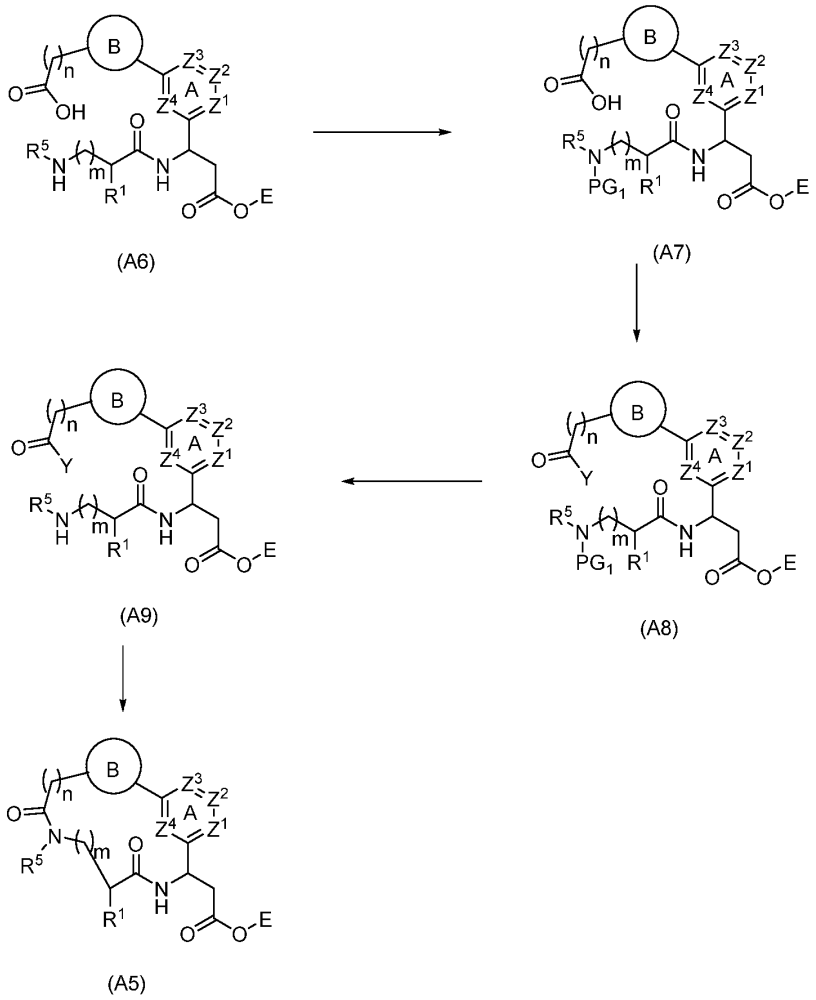
**[0089]** Compounds of formula (A1) in which L is -$C_{3-8}$alkylene-, where two adjacent methylene groups are substituted with -C(O)- and -N($R^5$)-, and n and m are zero to six (provided n and m combined is between one and six), which are compounds of formula (A5), may be prepared from intermediates of formula (A6), by an amide coupling. The amide coupling may be accomplished following the procedures for the formation of an amide bond described hereinafter. In particular, intermediates of formula (A6) may be treated with a coupling agent, for example N,N′-carbonyldiimidazole (CDI), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide (EDCI) or benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (commercially available as PyBOP), in a solvent such as tetrahydrofuran, dichloromethane, chloroform or 1,2-dichloroethane. The reaction is preferably conducted in the presence of a base such as triethylamine, diisopropylethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).



(A6) (A5)

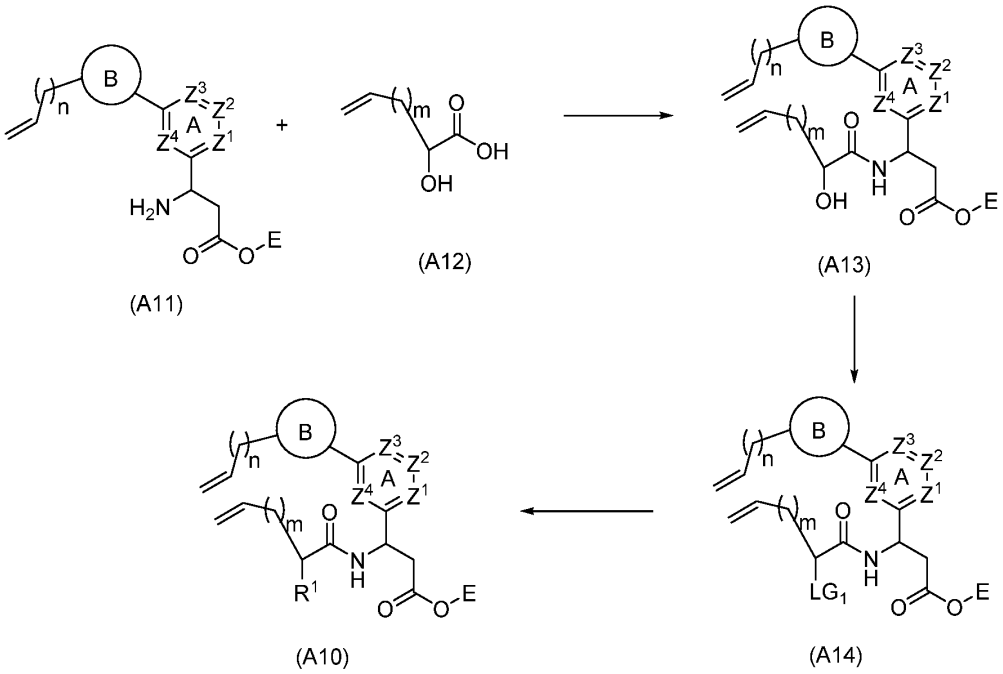
**[0090]** Intermediates of formula (A6) can also be converted into an activated form (A9), wherein Y represents halo or the rest of an active ester, for example Y is an aryloxy group such as phenoxy, p-nitrophenoxy, pentafluorophenoxy and the like, or Y can be the rest of a mixed anhydride. The activation of the carboxylic acid in (A6) may lead to an internal cyclisation reaction to give compounds of formula (A5).




**[0091]** Activated intermediates of formula (A9) can be prepared from intermediates of formula (A6) as outlined in the above scheme. The amine functionality in (A6) is protected with $PG_1$, where $PG_1$ represents a suitable amine protecting group (as defined above), to give intermediates of formula (A7). The carboxylic acid functionality in (A7) can then be activated, as described above, to give intermediates of formula (A8). Removal of the amine protecting group ($PG^1$), which can be done following known procedures in the art, gives intermediates of formula (A9) which undergo an internal cyclisation reaction to give compounds of formula (A5).

**[0092]** Intermediates of formula (A3) in which $R^1$ represents an N-linked group, such as $NR^8C(O)R^9$, or N-linked heterocyclyl group (such as pyrrolidin-2-onyl, piperidin-2-onyl, or 2-oxopyridin-1(2*H*)-yl) and where n, m and E are defined above, which are intermediates of formula (A10), may be prepared from intermediates of formula (A14), where $LG_1$ represents a suitable leaving group, for example mesylate, triflate, tosylate, bromide, chloride and the like. The reaction between intermediates of formula (A14) and N-linked heterocyclyl group may be

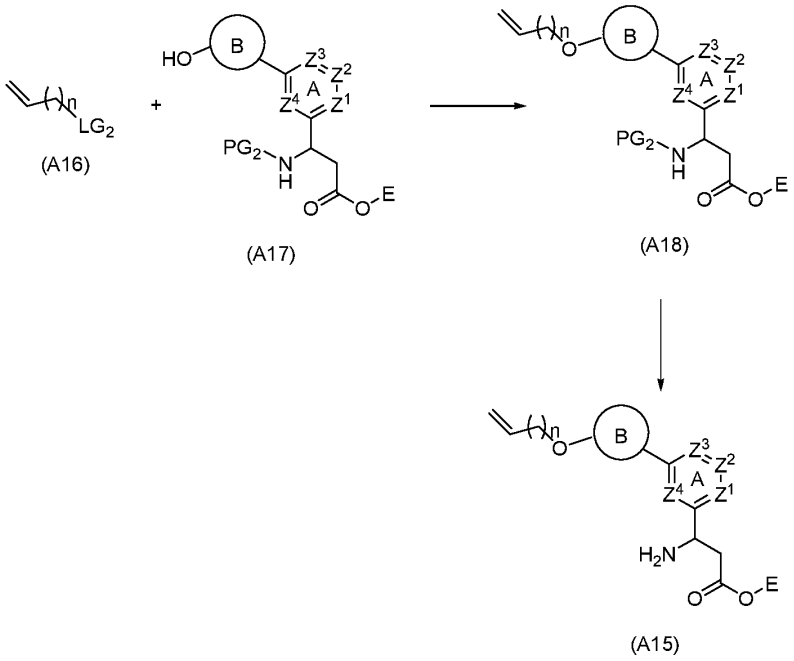
conducted in the presence of a base, for example sodium hydride, sodium methoxide, potassium tert-butoxide or potassium carbonate, and an inert solvent like dimethylacetamide, dimethylformamide, acetonitrile and the like.




**[0093]** Intermediates of formula (A14) can be obtained from intermediates of formula (A13) using methods well known to those of skill in the art. For example, mesylate, triflate, tosylate, bromine and chlorine leaving groups can be introduced by reacting the alcohol functionality in (A13) with, respectively, mesyl chloride, trifluoromesyl chloride, tosyl chloride, phosphorus tribromide and thionyl chloride in a solvent, such as diethyl ether, tetrahydrofuran, toluene or cyclohexane or mixtures thereof, in the presence of a base such as triethylamine, diisopropylethylamine or pyridine.

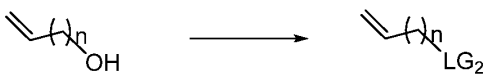
**[0094]** Intermediates of formula (A13) can be prepared by forming an amide bond between intermediates of formula (A11) and (A12) using the conditions described above for the preparation of intermediates of formula (A5) from intermediates of formula (A6). Intermediates of formula (A12) are commercially available or can be prepared according to methodologies known to the skilled in the art.

**[0095]** Intermediates of formula (A11), in which the methylene group attached to B has been replaced with -O-, and where n and E are defined above, which are intermediates of formula (A15), may be prepared from intermediates of formula (A16) and (A17), followed by deprotection of the amine protecting group ($PG_2$) in intermediates of formula (A18).



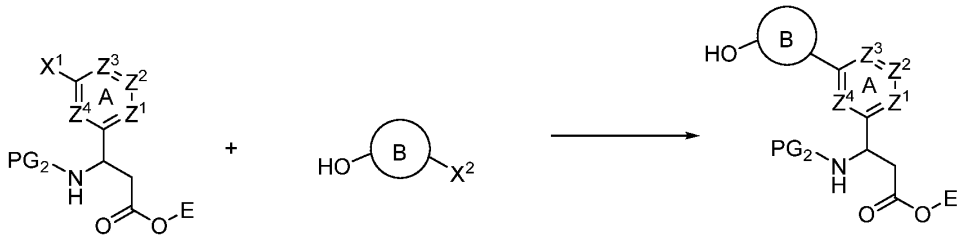

**[0096]** In the procedure of the above scheme, intermediates of formula (A16), wherein $LG_2$ represents a suitable leaving group such as mesylate, triflate, tosylate, bromine or chlorine, are coupled to the alcohol functionality in intermediates of formula (A17), where $PG_2$ represents a suitable amine protecting group, to form an ether linkage. The reaction may be conducted in the presence of a base, for example potassium carbonate, sodium hydride or potassium tert-butoxide, in an inert solvent like dimethylacetamide, dimethylformamide, acetonitrile and the like. Removal of the amine protecting group ($PG_2$) in intermediates of formula (A18) to give intermediates of formula (A15) can accomplished following procedures known in the art. For example, when a Boc group is used, the methods of choice are trifluoroacetic acid in dichloromethane or hydrochloric acid in 1,4-dioxane.

**[0097]** Intermediates of formula (A16) are commercially available, or can be prepared from intermediates of formula (A19) using the condition described above for the preparation of intermediates of formula (A14) from intermediates of formula (A13). Intermediates of formula (A19) are commercially available, or readily available through synthesis procedures known in the art.




**[0098]** Intermediates of formula (A17), where E and $PG_2$ are defined above, can be prepared by a transition metal catalysed cross-coupling reaction between intermediates of formula (A20) and intermediates of formula (A21), in which $X^1$ and $X^2$ represent a pair of reactive moieties

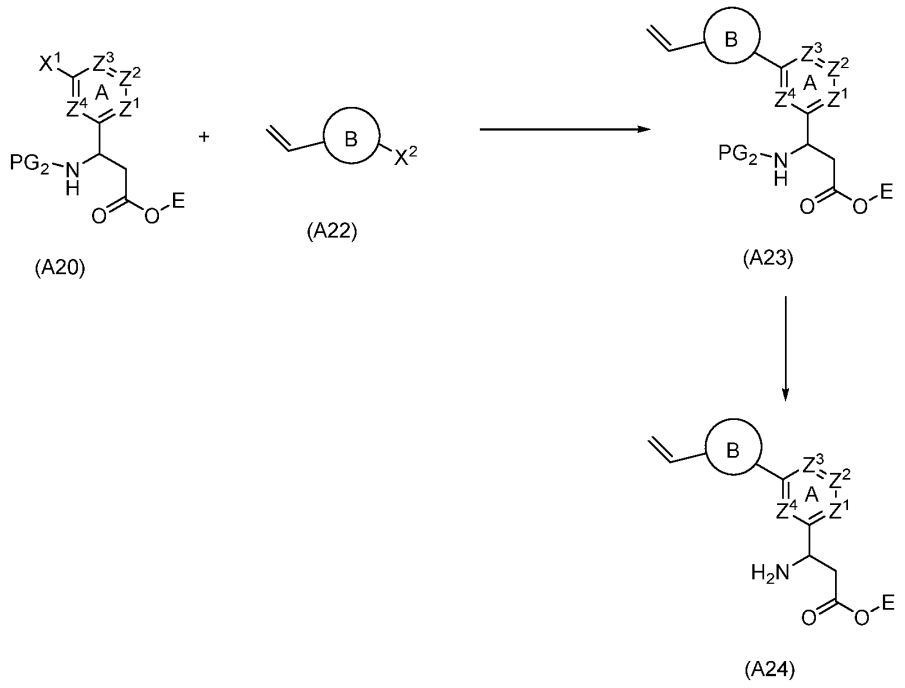
capable of undergoing a transition metal catalysed cross-coupling reaction. Exemplary reactive moieties include, but are not limited to, halide, triflate and boron-containing functional groups. When one of $X^1$ or $X^2$ is halide or triflate the other $X^1$ or $X^2$ is a boron-containing functional group of the formula $-B(OR)_2$, where each R can independently be hydrogen or alkyl. When R is alkyl, it is preferred that the two R substituents and boron atom form a ring (e.g., a pinacol boronic ester).



(A20) (A21) (A17)

**[0099]** The cross-coupling reaction can be conducted in the presence of a suitable catalyst, such as $Pd(PPh_3)_4$, $Pd_2(dba)_3$ or $Pd(dppf)Cl_2$ and a mild base, such as $K_2CO_3$ and $Na_2CO_3$, in a suitable solvent, such as 1,4-dioxane, toluene, ethanol, water and mixtures thereof, at an elevated temperature. The selection of catalyst, base, solvent and reaction conditions (i.e., time, temperature, pressure, choice of atmosphere, etc.) are known to those skilled in the art.

**[00100]** Intermediates of formula (A11), in which n is zero and E is defined above, which are intermediates of formula (A24), may be prepared from intermediates of formula (A20) and (A22), followed by deprotection of the amine protecting group ($PG_2$) in intermediates of formula (A23).

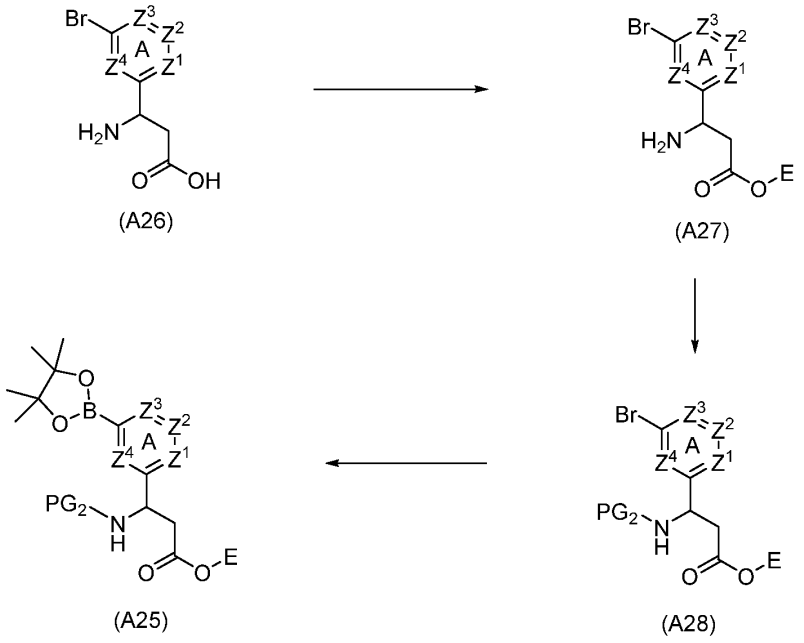


(A20) (A22) (A23) (A24)

**[00101]** In the procedure of the above scheme, the cross-coupling of intermediates of formula (A20) and (A22) to give intermediates of formula (A23) can be accomplished using the conditions described above for the cross-coupling of intermediates of formula (A20) and (A21) to give intermediates of formula (A17). Removal of the amine protecting group ($PG_2$) in intermediates of formula (A23) to give intermediates of formula (A24) can be accomplished using the conditions described above for the deprotection of intermediates of formula (A18) to give intermediates of formula (A15).

**[00102]** Intermediates of formula (A21) and (A22), where $X^2$ represents a reactive moiety capable of undergoing a transition metal catalysed cross-coupling reaction (e.g., halide, triflate, boronic acid and boronic ester) and B is defined according to the scope of the present invention, are commercially available, or can be prepared according to methodologies known to those skilled in the art.

**[00103]** Intermediates of formula (A20) where $X^1$ represents a pinacol boronic ester, which are intermediates of formula (A25), can be prepared from intermediates of formula (A26) by a process involving first protection of the acid functionality with a suitable protecting group (E) to give intermediates of formula (A27), followed by protection of the amine functionality in (A27) with a suitable protecting group ($PG_2$) to give intermediates of formula (A28) and then by a cross-coupling reaction with bis(pinacolato)diboron to give intermediates of formula (A25).

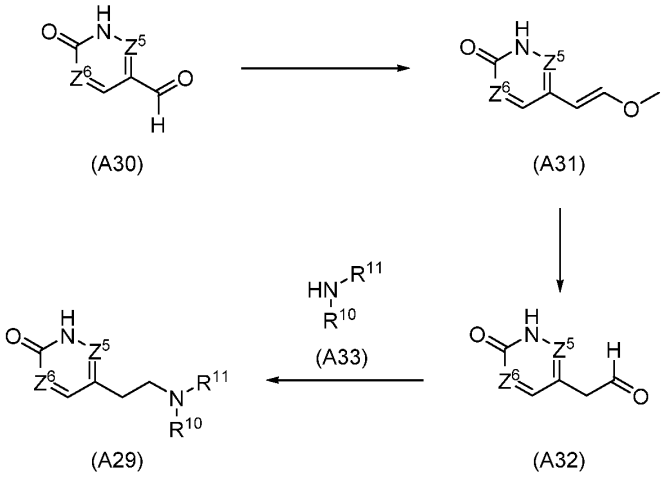



**[00104]** In the procedure of the above scheme, protection of the acid functionality in intermediates of formula (A26) with a suitable protecting group (E) to give intermediates of formula (A27) can be accomplished by reacting together intermediates of formula (A26) and a $C_{1\text{-}6}$alkyl alcohol (e.g.,

methanol or ethanol) with removal of water either physically, e.g. by azeotropical water removal or chemically by using a dehydrating agent. Protection of the amine functionality in intermediates of formula (A27) with a suitable protecting group ($PG_2$) to give intermediates of formula (A28) can be accomplished using the conditions described above for protection of the amine functionality in intermediates of formula (A6) to give intermediates of formula (A7). Conversion of the bromine functionality in intermediates of formula (A28) to the pinacol boronic ester functionality in (A25) can be accomplished using the conditions described above for the cross-coupling of intermediates of formula (A20) and (A21) to give intermediates of formula (A17).

**[00105]** The synthesis of intermediate β-amino acids of formula (A26), can be accomplished using well known procedures described in the literature, such as Enantioselective Synthesis of β-Amino Acids, (John Wiley & Sons, 2005); Ellman et.al., *Acc. Chem. Res.* 2002, 35, 984-995, Franklin A. Davis and Bang-Chi, Chen *Chem. Soc. Rev.*, 1998, 27, 13-18; Mikkel F. Jacobsen and Troels Skrydstrup, *J. Org. Chem.* 2003, 68, 7122; Tony P. Tang and Jonathan A. Ellman, *J. Org. Chem.* 2002, 67, 7819; and Tony P. Tang and Jonathan A. Ellman, *J. Org. Chem.* 1999, 64, 12.

**[00106]** 2-oxopyridin-1(2*H*)-yl ($Z^5$ and $Z^6$ are C), pyridazin-3(2H)-one ($Z^5$ is N and $Z^6$ is C) and pyrimidin-2(1H)-one ($Z^5$ is C and $Z^6$ is N) intermediates, used in the synthesis of intermediates of formula (A10), are commercially available or can be readily prepared according to methodologies known to those skilled in the art. For example, substituted intermediates of formula (A29), may be prepared from intermediates of formula (A30), wherein the ring may be further substituted with one or more optional substituents as described herein.

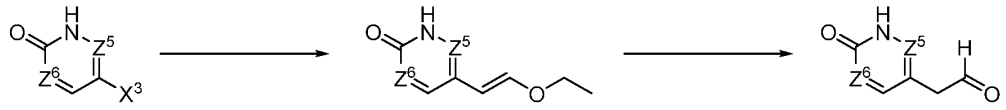



**[00107]** In the procedure of the above scheme, the aldehyde functionality in intermediates of formula (A30) may be subjected to a Wittig reaction using the Wittig reagent, (methoxymethyl)triphenylphosphonium chloride, in the presence of a strong base, such as sodium hydride or potassium tert-butoxide, in an inert solvent, such as dimethoxyethane or tetrahydrofuran, at or near room temperature to give intermediates of formula (A31). Cleavage of

the enol ether functionality in intermediates of formula (A31) can be accomplished by acid hydrolysis using for example trifluoroacetic acid or formic acid in a suitable solvent, such as dichloromethane, to give intermediates of formula (A32). Reductive amination of the aldehyde functionality in intermediates of formula (A32) with the amine functionality in intermediates of formula (A33) gives intermediates of formula (A29). The reductive amination may be conducted under acidic or neutral conditions (i.e., with or without acid present, e.g. acetic acid) in the presence of a suitable reducing agent, such as sodium triacetoxyborohydride, in a suitable solvent such as dichloromethane, 1,2-dichloroethane, tetrahydrofuran or mixtures thereof.

**[00108]** Intermediates of formula (A30) and (A33) are commercially available, or readily available through synthesis procedures known in the art.

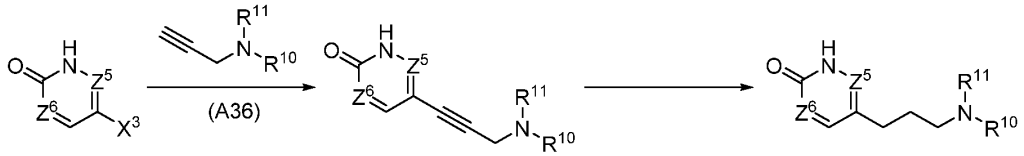
**[00109]** Intermediates of formula (A32) can also be prepared from intermediates of formula (A33), in which $X^3$ represents a triflate or halide group, by a process involving first a transition metal catalysed cross-coupling reaction with *trans*-2-ethoxyvinylboronic acid pinacol ester to give intermediates of formula (A34), using the conditions described above for the cross-coupling of intermediates of formula (A20) and (A21) to give intermediates of formula (A17), followed by cleavage of the enol ether functionality in intermediates of formula (A34) to give intermediates of formula (A32) using the conditions described above for the conversion of intermediates of formula (A31) to intermediates of formula (A32).



(A33) (A34) (A32)

**[00110]** Intermediates of formula (A33) are commercially available, or readily available through synthesis procedures known in the art.

**[00111]** Substituted 2-oxopyridin-1(2*H*)-yl ($Z^5$ and $Z^6$ are C), pyridazin-3(2H)-one ($Z^5$ is N and $Z^6$ is C) and pyrimidin-2(1H)-one ($Z^5$ is C and $Z^6$ is N) intermediates of formula (A35), may be prepared from intermediates of formula (A33), wherein the ring may be further substituted with one or more optional substituents as described herein and $X^3$ represents a triflate or halide group.



(A33) (A36) (A37) (A35)

**[00112]** In the procedure of the above scheme, the cross-coupling of intermediates of formula (A33) and (A36) to give intermediates of formula (A37) can be accomplished in the presence

of a suitable catalyst, such as $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$, a copper salt, typically copper(I) iodide, and a base such as triethylamine. The reaction is carried out in a solvent, such as THF or 1,4-dioxane, at an elevated temperature. Intermediates of formula (A35) may be prepared from intermediates of formula (A37), by reduction of the triple bond. The reduction may be accomplished by catalytic hydrogenation with hydrogen in the presence of a noble metal catalyst such as Pt, Pd, Rh, Ru or Raney nickel. The hydrogenation reaction is conducted in a solvent such as methanol, ethanol, tetrahydrofuran or mixtures thereof.

**[00113]** Intermediates of formula (A36) are commercially available, or readily available through synthesis procedures known in the art.

Pharmaceutical Compositions

**[00114]** The compounds of the invention will normally, but not necessarily, be formulated into pharmaceutical compositions prior to administration to a patient. Therefore, according to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of Formula I as defined hereinbefore, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

**[00115]** The pharmaceutical compositions of the invention may be prepared and packaged in bulk form wherein a safe and effective amount of a compound of the invention can be extracted and then given to the patient such as with powders or syrups. Alternatively, the pharmaceutical compositions of the invention may be prepared and packaged in unit dosage form wherein each physically discrete unit contains a safe and effective amount of a compound of the invention. When prepared in unit dosage form, the pharmaceutical compositions of the invention typically contain from 1 mg to 1000 mg.

**[00116]** The compositions of the invention may be in a form suitable for oral use (for example as tablets, capsules, caplets, pills, troches, powders, syrups, elixirs, suspensions, solutions, emulsions, sachets, and cachets), for topical use (for example as creams, ointments, lotions, solutions, pastes, sprays, foams, and gels), for transdermal administration such as *via* transdermal patches, for administration by inhalation (for example as a dry powders, aerosols, suspensions, and solutions), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

**[00117]** In a convenient embodiment, the pharmaceutical composition of the present invention is in a form suitable for parenteral administration, such as intravenous or intraperitoneal administration. Solutions or suspensions used for parenteral administration may comprise one or more of the following excipients: sterile diluent (e.g. water, saline, oils,

glycerine, propylene glycol, polyethylene glycols, or other pharmaceutically acceptable solvents); buffer agent (e.g. acetates, citrates, phosphates, or tonicity adjusters such as sodium chloride or dextrose); chelating agent (e.g. edta); antibacterial agent (e.g. methyl parabens or benzyl alcohol); or antioxidant (e.g. ascorbic acid or sodium bisulfite). In a convenient embodiment, the pharmaceutical composition of the present invention is in a form suitable for intravenous or intraperitoneal administration and comprises phosphate buffered saline or physiological saline. Conveniently, the parenteral composition is enclosed within ampoules, vials, or syringes made from either glass or plastic.

**[00118]** As used herein, "pharmaceutically-acceptable excipient" means a pharmaceutically acceptable material, composition or vehicle involved in giving form or consistency to the pharmaceutical composition. Each excipient must be compatible with the other ingredients of the pharmaceutical composition when commingled such that interactions which would substantially reduce the efficacy of the compound of the invention when administered to a patient and interactions which would result in pharmaceutical compositions that are not pharmaceutically acceptable are avoided. In addition, each excipient must be of sufficiently high purity to render it pharmaceutically-acceptable.

**[00119]** Suitable pharmaceutically-acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically-acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the carrying or transporting of the compound or compounds of the invention once administered to the patient from one organ, or portion of the body, to another organ, or portion of the body. Certain pharmaceutically-acceptable excipients may be chosen for their ability to enhance patient compliance.

**[00120]** Suitable pharmaceutically-acceptable excipients include the following types of excipients: diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavoring agents, flavor masking agents, coloring agents, anticaking agents, humectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents. The person skilled in the art will appreciate that certain pharmaceutically-acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other ingredients are present in the formulation.

**[00121]** Persons skilled in the art possess the knowledge and skill to enable them to select suitable pharmaceutically-acceptable excipients in appropriate amounts for use in the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically-acceptable excipients and may be useful in selecting suitable pharmaceutically-acceptable excipients. Examples include Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press).

**[00122]** The pharmaceutical compositions of the invention are prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

**[00123]** The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

**[00124]** The size of the dose for therapeutic or prophylactic purposes of a compound of the formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

**[00125]** In using a compound of the invention for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general, lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous or intraperitoneal administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration may also be suitable, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

Routes of Administration

**[00126]** The compounds of the invention or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/peripherally or topically (i.e. at the site of desired action).

**[00127]** Routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eyedrops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., *via* an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

**[00128]** In a preferred embodiment, a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, is administered orally, intravenously, subcutaneously or intramuscularly.

Therapeutic Uses and Applications

**[00129]** The compounds of the invention are inhibitors of the α4β7 integrin. As a consequence, they are potentially useful therapeutic agents for the treatment of diseases or conditions mediated by α4β7 inhibition.

**[00130]** Thus, in one aspect, the present invention relates to a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in therapy.

**[00131]** In another aspect, the present invention relates to a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a disease or disorder mediated by inhibition of α4β7.

**[00132]** In another aspect, the present invention relates to the use of a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of diseases or disorders mediated by α4β7 inhibition.

**[00133]** In another aspect, the present invention relates to a method of treating a disease or disorder mediated by inhibition of α4β7, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

**[00134]** Examples of inflammatory diseases that the compounds of Formula I and their pharmaceutically acceptable salts may be used to treat are inflammatory bowel diseases such as ulcerative colitis or Crohn's disease, eosinophilic gastrointestinal diseases, and pouchitis.

**[00135]** In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of inflammatory bowel diseases such as ulcerative colitis or Crohn's disease.

**[00136]** In another aspect, the present invention provides the use of a compound, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of inflammatory bowel diseases such as ulcerative colitis or Crohn's disease.

**[00137]** In another aspect, the present invention provides a method of treating inflammatory bowel diseases such as ulcerative colitis or Crohn's disease, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

**[00138]** In another aspect, the present invention provides a method of inhibiting α4β7 *in vitro*, said method comprising administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof.

**[00139]** In another aspect, the present invention provides a method of inhibiting α4β7 *in vivo*, said method comprising administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof.

**[00140]** In another aspect, the present invention provides a method of inhibiting α4β7 *in vitro* and/or *in vivo*, said method comprising contacting a cell with an effective amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof.

Combination Therapy

**[00141]** The compounds of the invention may be administered alone as a monotherapy or may administered in combination with one or more additional therapeutic agents. The selection of the one or more additional therapeutic agents will of course vary depending on the disease or condition to be treated and its severity.

**[00142]** It is commonplace to use combination therapies to treat certain medical conditions.

**[00143]** According to a particular aspect of the invention there is provided a combination suitable for use in the treatment of a disease or condition in which α4β7 inhibition is implicated, comprising a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt thereof, and another therapeutic agent.

**[00144]** According to this aspect of the invention there is provided a combination suitable for use in the prevention or treatment of an inflammatory bowel disease such as ulcerative colitis or Crohn's disease, the combination comprising a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents.

**[00145]** In a further aspect of the invention there is provided a compound of the invention or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents.

**[00146]** Herein, where the term "combination" is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention "combination" refers to simultaneous administration. In another aspect of the invention "combination" refers to separate administration. In a further aspect of the invention "combination" refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

**[00147]** According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the invention, or a pharmaceutically acceptable salt thereof in combination with one or more additional therapeutic agents in association with a pharmaceutically acceptable diluent or carrier.

**[00148]** The one or more additional therapeutic agents may comprise a further compound of the present invention. Therefore, in an embodiment, there is provided a pharmaceutical composition which comprises two compounds of the invention, or pharmaceutically acceptable salts thereof, in association with a pharmaceutically acceptable diluent or carrier.

**[00149]** Examples of other therapeutic agents that may be used as part of a combination therapy with a compound of the present invention (e.g. as one of two or more active agents as part of double or triple combinations) include, but are not limited to, the following:

i) Aminosalicylates (5-ASAs), including sulphasalazine, mesalazine, balsalazide and olsalazine;

ii) Steroids, including prednisolone, hydrocortisone, methylprednisolone, beclomethasone dipropionate, budesonide and budesonide-MMX

iii) Immunosuppressants, including azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus and methotrexate;

iv) Anti-TNF Biologics, including infliximab, adalimumab, certolizumab and golimumab;

v) Anti-IL-12/IL-23 Biologics, including ustekinumab, mirikizumab and risankizumab

vi) Anti-a4b7 biologics, including vedolizumab

vii) JAK kinase inhibitors, including filgotinib, upadacitinib and tofacitinib

viii) S1P receptor modulators, including ozanimod, etrasimod and fingolimod

ix) Anti-diarrhoeals, including loperamide, codeine phosphate and diphenoxylate

x) Antispasmodics, including mebeverine, hyoscine butylbromide and alverine citrate

xi) Antibiotics, including metronidazole, ampicillin, ciprofloxacin

**[00150]** The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention.

**[00151]** Such conjoint/combination treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. In one embodiment, the individual compounds will be administered simultaneously in a combined pharmaceutical formulation.

**[00152]** Such combination therapies employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent within approved dosage ranges and/or the dosage such as described in the relevant publication reference.

## EXAMPLES

**[00153]** Methods for preparing the compounds of this invention are illustrated in the following Examples. Starting materials are made according to procedures known in the art or as illustrated herein or are available commercially. Commercial reagents were used without further purification. Where no reaction temperature is included, the reaction was performed at ambient temperature which is typically 17–27 °C.

**[00154]** A person skilled in the art will appreciate that reaction temperatures, reaction times and reagent quantities may be varied from those stated herein.

**[00155]** Flash chromatography carried out using Combiflash® Nextgen 300+ and automated reverse-phase chromatography carried out on Interchim Puriflash® 4100

**[00156]** Where compounds described in the invention are characterized by $^{1}$H NMR spectroscopy, Bruker 500 MHz spectrometer instrument or Bruker Ultrashield 400 MHz spectrometer. Where no temperature is included, the spectra were recorded at ambient temperature. Chemical shift values are expressed in parts per million (ppm). The following

abbreviations are used for the multiplicity of the NMR signals: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad.

**[00157]** Where compounds described in the invention are characterized by LCMS data, retention time and molecular weight are determined using the conditions listed below.

**Method 1:** Waters Acquity HT with diode array (210-350 nm) and ZQ mass detector. Column: YMC Triart C18 5 µm 2.0 x 50 mm (Flow 0.8 mL/min) at 50 °C. Conditions: Water with 0.05% formic acid [eluent A], MeCN [eluent B]. Gradient: 0 - 95% B over 4.0 min, hold at 98% B for 0.5 min.

**Method 2:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC CSH C18 1.7 µm 2.1 x 50 mm (Flow 1.0 mL/min) at 50 °C. Conditions: Water with 0.05% formic acid [eluent A], MeCN [eluent B]. 2% B 0.2 min, gradient: 2 - 98% B over 2.3 min, hold at 98% B for 0.7 min.

**Method 3:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.8 mL/min) at 50 °C. Conditions: Water with 0.05% formic acid [eluent A], MeCN [eluent B]. Gradient: 0 - 95% B over 1.7 min, hold at 95% B for 0.4 min.

**Method 4:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.8 mL/min) at 50 °C. Conditions: Water with 0.05% ammonia [eluent A], MeCN [eluent B]. Gradient: 0 - 95% B over 1.7 min, hold at 95% B for 0.4 min.

**Method 5:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 1.0 mL/min) at 50 °C. Conditions: Water with 0.05% ammonia [eluent A], MeCN [eluent B]. Gradient: 2 - 98% B over 2.3 min, hold at 98% B for 3.0 min.

**Method 6:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.8 mL/min) at 50 °C. Conditions: Water with 0.05% formic acid [eluent A], MeCN [eluent B]. Gradient: 2 - 98% B over 1.8 min, hold at 98% B for 0.3 min.

**Method 7:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.8 mL/min) at 50 °C. Conditions: Water with 0.05% formic acid [eluent A], MeCN [eluent B]. Gradient: 0 - 95% B over 2.50 min, hold at 95% B for 0.8 min.

**Method 8:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 1.0 mL/min) at 50 °C. Conditions: Water with 0.1% formic acid [eluent A], MeCN [eluent B]. 2% B 0.2 min, gradient: 2 - 98% B over 2.3 min, hold at 98% B for 0.8 min.

**Method 9:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 1.0 mL/min) at 50 °C. Conditions: Water with 0.1% formic acid [eluent A], MeCN [eluent B]. 50% B 0.5 min, gradient: 50 - 98% B over 6.0 min, hold at 98% B for 1.0 min.

**Method 10:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.6 mL/min) at 50 °C. Conditions: Water with 0.1% ammonia [eluent A], MeCN [eluent B]. 2% B 0.5 min, gradient: 2 - 98% B over 6.0 min, hold at 98% B for 1.0 min.

**Method 11:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.6 mL/min) at 50 °C. Conditions: Water with 0.1% ammonia [eluent A], MeCN [eluent B]. 2% B 0.2 min, gradient: 2 - 98% B over 2.3 min, hold at 98% B for 0.8 min.

**Method 12:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.8 mL/min) at 50 °C. Conditions: Water with 0.1% ammonia [eluent A], MeCN [eluent B]. Gradient: 2 - 98% B over 1.8 min, hold at 98% B for 0.3 min.

**Method 13:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 1.0 mL/min) at 50 °C. Conditions: Water with 0.1% formic acid [eluent A], MeCN [eluent B]. 2% B 0.2 min, gradient: 2 - 98% B over 2.3 min, hold at 98% B for 0.8 min.

**Method 14:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 1.0 mL/min) at 50 °C. Conditions: Water with 0.1% ammonia [eluent A], MeCN [eluent B]. 5% B 0.5 min, gradient: 5 - 95% B over 6 min, hold at 95% B for 1 min.

**Method 15:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.8 mL/min) at 50 °C. Conditions: Water with 0.1% ammonia [eluent A], MeCN [eluent B]. Gradient: 0 - 95% B over 2.5 min, hold at 95% B for 0.8 min.

**Method 16:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 1.0 mL/min) at 50 °C. Conditions: Water with 0.1% formic acid [eluent A], MeCN [eluent B]. 5% B 0.5 min, gradient: 5 - 95% B over 6 min, hold at 95% B for 1 min.

**Method 17:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.8 mL/min) at 50 °C. Conditions: Water with 0.05% ammonia [eluent A], MeCN [eluent B]. Gradient: 0 - 95% B over 2.5 min, hold at 95% B for 0.5 min.

**Method 18:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.8 mL/min) at 50 °C. Conditions: Water with 0.05% formic acid [eluent A], MeCN [eluent B]. Gradient: 0 - 95% B over 1.70 min, hold at 95% B for 0.4 min.

**Method 19:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 1.0 mL/min) at 50 °C. Conditions: Water with 0.1% ammonia [eluent A], MeCN [eluent B]. 0% B 0.5 min, gradient: 0 - 98% B over 6 min, hold at 98% B for 1 min.

**Method 20:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 1.0 mL/min) at 50 °C. Conditions: Water with 0.1% formic acid [eluent A], MeCN [eluent B]. 2% B 0.5 min, gradient: 2 - 98% B over 6 min, hold at 98% B for 1 min.

**Method 21:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 1.0 mL/min) at 50 °C. Conditions: Water with 0.1% ammonia [eluent A], MeCN [eluent B]. 0% B 0.5 min, gradient: 0 - 95% B over 6 min, hold at 95% B for 1 min.

**Method 22:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.8 mL/min) at 50 °C. Conditions: Water with 0.1% ammonia [eluent A], MeCN [eluent B]. Gradient: 0 - 95% B over 1.7 min, hold at 95% B for 0.4 min.

**Method 23:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.6 mL/min) at 50 °C. Conditions: Water with 0.1% formic acid [eluent A], MeCN [eluent B]. Gradient: 2 - 98% B over 2.50 min, hold at 98% B for 0.8 min.

**Method 24:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.8 mL/min) at 50 °C. Conditions: Water with 0.1% formic acid [eluent A], MeCN [eluent B]. 0% B 0.5 min, gradient: 0 - 95% B over 6 min, hold at 95% B for 1 min.

**Method 25:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.8 mL/min) at 50 °C. Conditions: Water with 0.1% ammonia [eluent A], MeCN [eluent B]. Gradient: 10 - 95% B over 3.5 min, hold at 95% B for 0.9 min.

**Method 26:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.6 mL/min) at 50 °C. Conditions: Water with 0.1% formic acid [eluent A], MeCN [eluent B]. Gradient: 15 - 98% B over 4 min, hold at 98% B for 0.8 min.

**Method 27:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.8 mL/min) at 50 °C. Conditions: Water with 0.1% ammonia [eluent A], MeCN [eluent B]. Gradient: 50 - 95% B over 3.5 min, hold at 95% B for 0.9 min.

**Method 28:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.6 mL/min) at 50 °C. Conditions: Water with 0.1% ammonia [eluent A], MeCN [eluent B]. Gradient: 15 - 98% B over 4.0 min, hold at 98% B for 0.8 min.

**Method 29:** Waters Acquity H class UPLC with diode array (210-350 nm) and QDa mass detector. Column: Acquity UPLC BEH C18 1.7 µm 2.1 x 50 mm (Flow 0.6 mL/min) at 50 °C. Conditions: Water with 0.1% formic acid [eluent A], MeCN [eluent B]. 2% B 0.5 min, gradient: 2 - 98% B over 6 min, hold at 98% B for 1 min.

**[00158]** Preparative HPLC was performed using Waters 2545 Binary Gradient Module with 2998 PDA and 2767 Sample Manager, Waters SFO module.

Abbreviations

| | |
|---|---|
| AcOH | Acetic acid |
| $BF_3.OEt_2$ | Boron trifluoride diethyl etherate |
| Boc | tert-Butyloxycarbonyl |
| CAN | Ceric ammonium nitrate |
| CDI | 1,1'-Carbonyldiimidazole |
| $Co(acac)_2$ | Cobalt (II) acetylacetonate |
| $Cs_2CO_3$ | Cesium carbonate |
| DCE | 1,2-Dichloroethane |
| DCM | Dichloromethane |
| DIAD | Diisopropyl azodicarboxylate |
| DIPEA | N,N-Diisopropylethylamine |
| DME | 1,2-Dimethoxyethane |
| DMF | N,N-Dimethylformamide |
| DMSO | Dimethylsulfoxide |
| EDCI | N-Ethyl-N′-(3-dimethylaminopropyl)carbodiimide hydrochloride |
| EtOAc | Ethyl acetate |
| Grubbs II | Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium |
| Grubbs M204 | [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(benzylidene)(tricyclohexylphosphine)ruthenium(II) |
| Hoveyda-Grubbs M720 | (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium |
| h | Hour(s) |
| HBr | Hydrogen bromide |
| HCl | Hydrogen chloride |
| HOBt | Hydroxybenzotriazole |
| HPLC | High Performance Liquid Chromatography |
| IPA | Isopropyl alcohol |
| $K_2CO_3$ | Potassium carbonate |
| $K_3PO_4$ | Potassium phosphate |

| | |
|---|---|
| LCMS | Liquid Chromatography Mass Spectrometry |
| MeCN | Acetonitrile |
| MeOH | Methanol |
| $MgSO_4$ | Magnesium sulfate |
| min | Minute(s) |
| $Na_2CO_3$ | Sodium carbonate |
| $NaHCO_3$ | Sodium bicarbonate |
| $Na_2SO_4$ | Sodium sulfate |
| $NH_4Cl$ | Ammonium chloride |
| NMR | Nuclear Magnetic Resonance |
| $Pd(dppf)Cl_2$ | 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride |
| $Pd(dtbpf)Cl_2$ | [1,1′-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) |
| $Pd(PPh_3)_4$ | Tetrakis(triphenylphosphine)palladium(0) |
| $Pd(PPh_3)_2Cl_2$ | Dichlorobis(triphenylphosphine)palladium(II) |
| RT | Room temperature |
| RuPhos | 2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl |
| RuPhosPdG3 | (2-Dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1-biphenyl)]palladium(II) methanesulfonate |
| s | Second(s) |
| SPhos | 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl |
| STAB | Sodium triacetoxyborohydride |
| TBAF | Tetrabutylammonium fluoride trihydrate |
| tBu | Tertiary butyl |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| Xantphos | 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene |
| XPhosPdG2 | Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) |

## Synthesis of Intermediates

**Intermediate 1:** Methyl (*S*)-3-(3-bromophenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00159]** To a stirred suspension of methyl (*S*)-3-amino-3-(3-bromophenyl)propanoate hydrochloride (12.1 g, 41.1 mmol, CAS 1391379-45-5) and triethylamine (6.23 g, 61.6 mmol) in DCM (28.5 mL) was added Boc anhydride (9.86 g, 45.2 mmol) and the reaction mixture stirred for 20 h at RT. The reaction mixture was diluted with water and the crude product extracted into DCM. The combined organics were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide the title compound (15.5 g). $^1$H NMR (500 MHz; $CDCl_3$) δ: 7.46 (s, 1H), 7.41 (d, 1H), 7.26 – 7.20 (m, 2H), 5.56 (br s, 1H), 5.08 (br s, 1H), 3.65 (s, 3H), 2.84 (br s, 2H), 1.45 (br s, 9H).

**Intermediate 2:** Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate

**[00160]** A solution of **Intermediate 1** (14.7 g, 37.0 mmol) and bis(pinacolato)diboron (10.33 g, 40.68 mmol) in 1,4-dioxane (125 mL) was degassed with nitrogen. To the solution was then added potassium acetate (9.07 g, 92.5 mmol) followed by $Pd(dppf)Cl_2$ (2.71 g, 3.70 mmol) and the reaction mixture stirred at 95 °C for 20 h. The mixture was cooled and filtered through Celite®, washing with EtOAc and water. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash

chromatography (silica gel, eluting 50% EtOAc in petroleum ether) to provide the title compound (7.0 g). LCMS (Method 1): 3.55 min, 406.1 $[M+H]^+$.

**Intermediate 3:** Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00161]** A mixture of **Intermediate 2** (14.7 g, 37.0 mmol), 2-bromo-3-methylphenol (0.67 g, 3.60 mmol, CAS 22061-78-5) and $NaHCO_3$ (0.80 g, 7.56 mmol) in toluene (25 mL) and ethanol (5 mL) and water (5.5 mL) was degassed with nitrogen. To this was added $Pd(PPh_3)_4$ (0.21 g, 0.18 mmol) and the reaction mixture stirred at 85 °C for 16 h. The mixture was diluted with water and extracted into EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (24 g silica gel, eluting 20 - 50% EtOAc in petroleum ether) to provide the title compound (1.12 g). LCMS (Method 2): 2.07 min, 408.1 $[M+Na]^+$.

**Intermediate 4:** Methyl (*S*)-3-amino-3-(2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00162]** A suspension of **Intermediate 3** (0.19 g, 0.48 mmol) in 4 M HCl in 1,4-dioxane (3.0 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.15 g). LCMS (Method 2): 1.31 min, 286.2 $[M+H]^+$.

**Intermediate 5:** Methyl (*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enamido)-3-(2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00163]** To a solution of **Intermediate 4** (0.76 g, 2.37 mmol) and *N*-Boc-(S)-allylglycine (0.51 g, 2.37 mmol, CAS 90600-20-7) in DMF (5 mL) was added DIPEA (0.83 mL, 4.74 mmol), HOBt (0.44 g, 4.74 mmol) and EDCI (0.55 g, 2.85 mmol) and the mixture was stirred at RT for 4 h. The mixture was diluted with water and extracted into EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (24 g silica gel, eluting 30 - 50% EtOAc in petroleum ether) to provide the title compound (0.78 g). LCMS (Method 3): 1.63 min, 427.1 $[M-t\text{Bu}+H]^+$.

**Intermediate 6:** Methyl (*S*)-3-(2'-(but-3-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enamido)propanoate

**[00164]** To a suspension of **Intermediate 5** (0.78 g, 1.61 mmol) and $K_2CO_3$ (0.56 g, 4.02 mmol) in MeCN (5 mL) was added 4-bromobut-1-ene (0.33 mL, 3.22 mmol) and the mixture was stirred at reflux for 16 h. Additional 4-bromobut-1-ene (0.33 mL, 3.22 mmol) was added and stirring continued at reflux for 24 h. The mixture was diluted with water and extracted into EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (24 g silica gel, eluting 30-

50% EtOAc in petroleum ether) to provide the title compound (0.68 g). LCMS (Method 3): 1.90 min, 537.2 $[M+H]^+$.

**Intermediate 7:** Methyl 2-((9*S*,12*S*)-9-((*tert*-butoxycarbonyl)amino)-2$^6$-methyl-10-oxo-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphan-6-en-12-yl)acetate

**[00165]** A solution of **Intermediate 6** (0.27 g, 0.51 mmol) in DCE (4 mL) was degassed with nitrogen. To this was added Grubbs II (43 mg, 0.05 mmol) as a solution in degassed DCE (4 mL) and the mixture was stirred at 40 °C for 4 h. The mixture was cooled, and ethyl vinyl ether (0.05 mL, 0.51 mmol) was added and concentrated under reduced pressure. The crude product was purified by flash chromatography (24 g silica gel, eluting 30-50% EtOAc in petroleum ether) to provide the title compound (0.25 g). LCMS (Method 3): 1.78 min, 509.2 $[M+H]^+$.

**Intermediate 8:** Methyl 2-((9*S*,12*S*)-9-((*tert*-butoxycarbonyl)amino)-2$^6$-methyl-10-oxo-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetate

**[00166]** A solution of **Intermediate 7** (0.25 g, 0.49 mmol) in MeOH (5 mL) was added 5% palladium on carbon (52 mg) and the reaction was stirred under a hydrogen atmosphere at RT for 2 h. The mixture was filtered through Celite®, washing with MeOH and the filtrate was concentrated under reduced pressure to provide the title compound (0.22 g). LCMS (Method 3): 1.79 min, 511.1 $[M+H]^+$.

**Intermediate 9:** Methyl 2-((9*S*,12*S*)-9-amino-2$^6$-methyl-10-oxo-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetate hydrochloride

**[00167]** A suspension of **Intermediate 8** (0.22 g, 0.44 mmol) in 4 M HCl in 1,4-dioxane (5.0 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (0.22 g). LCMS (Method 2): 1.26 min, 411.2 $[M+H]^+$.

**Intermediate 10:** Methyl 2-((9*S*,12*S*)-9-acetamido-2$^6$-methyl-10-oxo-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetate

**[00168]** To a solution of **Intermediate 9** (0.20 g, 0.44 mmol) and triethylamine (0.13 mL, 0.96 mmol) in DCM (4 mL) was added acetyl chloride (0.03 mL, 0.48 mmol) and the mixture was stirred at RT for 20 min. The mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g silica gel, eluting 0 - 10% MeOH in DCM) to provide the title compound (0.15 g). LCMS (Method 3): 1.53 min, 453.2 $[M+H]^+$.

**Intermediate 11:** Methyl (*S*)-3-(2'-(allyloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enamido)propanoate

**[00169]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 5** (0.72 g, 1.48 mmol), $K_2CO_3$ (0.51 g, 3.71 mmol) and allyl bromide (0.26 mL, 2.97 mmol) in MeCN (20 mL) at RT for 72 h. Purified by flash chromatography (24 g silica gel, eluting 30 - 50% EtOAc

in petroleum ether) to provide the title compound (0.60 g). LCMS (Method 3): 1.84 min, 523.2 $[M+H]^+$.

**Intermediate 12:** Methyl 2-((8*S*,11*S*)-8-((*tert*-butoxycarbonyl)amino)-$2^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphan-5-en-11-yl)acetate

**[00170]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 11** (0.24 g, 0.46 mmol) in DCE (2 mL) and Grubbs II (39 mg, 0.05 mmol) in DCE (2 mL) at 40 °C for 4 h. Quenched with ethyl vinyl ether (0.04 mL, 0.46 mmol). Purified by flash chromatography (24 g silica gel, eluting 30-50% EtOAc in petroleum ether) to provide the title compound (0.23 g). LCMS (Method 3): 1.70 min, 495.1 $[M+H]^+$.

**Intermediate 13:** Methyl 2-((8*S*,11*S*)-8-((*tert*-butoxycarbonyl)amino)-$2^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetate

**[00171]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 12** (0.23 g, 0.47 mmol) and 5% palladium on carbon (50 mg) in MeOH (5 mL) under a hydrogen atmosphere at RT for 2 h to provide the title compound (0.18 g). LCMS (Method 3): 1.71 min, 497.1 $[M+H]^+$.

**Intermediate 14:** Methyl 2-((8*S*,11*S*)-8-amino-$2^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetate hydrochloride

**[00172]** A suspension of **Intermediate 13** (0.18 g, 0.37 mmol) in 4 M HCl in 1,4-dioxane (4.0 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (0.16 g). LCMS (Method 3): 1.19 min, 397.2 $[M+H]^+$.

**Intermediate 15:** Methyl 2-((8*S*,11*S*)-8-acetamido-$2^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetate

**[00173]** Prepared in an analogous manner to **Intermediate 10** using **Intermediate 14** (0.16 g, 0.37 mmol), triethylamine (0.11 mL, 0.81 mmol), acetyl chloride (0.03 mL, 0.41 mmol) in DCM (5 mL) at RT for 30 min. Purified by flash chromatography (12 g silica gel, eluting 0 - 10% MeOH in DCM) to provide the title compound (0.12 g). LCMS (Method 3): 1.45 min, 439.1 $[M+H]^+$.

**Intermediate 16:** Methyl (*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enamido)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00174]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 5** (0.72 g, 1.48 mmol), $K_2CO_3$ (0.51 g, 3.71 mmol) and 5-bromopent-1-ene (0.35 mL, 2.97 mmol) in MeCN (20 mL) at RT for 72 h. Purified by flash chromatography (24 g silica gel, eluting 30 - 50% EtOAc in petroleum ether) to provide the title compound (0.59 g). LCMS (Method 3): 1.96 min, 551.2 $[M+H]^+$.

**Intermediate 17:** Methyl 2-((10*S*,13*S*)-10-((*tert*-butoxycarbonyl)amino)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00175]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 16** (0.24 g, 0.43 mmol) in DCE (3 mL) and Grubbs II (36 mg, 0.04 mmol) in DCE (3 mL) at 40 °C for 4 h. Quenched with ethyl vinyl ether (2.0 mL, 20.1 mmol). Purified by flash chromatography (24 g silica gel, eluting 30-50% EtOAc in petroleum ether) to provide the title compound (0.21 g). LCMS (Method 3): 1.82 min, 523.2 $[M+H]^+$.

**Intermediate 18:** Methyl 2-((10*S*,13*S*)-10-((*tert*-butoxycarbonyl)amino)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00176]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 17** (0.21 g, 0.41 mmol) and 5% palladium on carbon (43 mg) in MeOH (5 mL) under a hydrogen atmosphere at RT for 2 h to provide the title compound (0.21 g). LCMS (Method 3): 1.86 min, 525.2 $[M+H]^+$.

**Intermediate 19:** Methyl 2-((10*S*,13*S*)-10-amino-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate hydrochloride

**[00177]** A suspension of **Intermediate 18** (0.21 g, 0.39 mmol) in 4 M HCl in 1,4-dioxane (6 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (0.18 g). LCMS (Method 3): 1.26 min, 425.2 $[M+H]^+$.

**Intermediate 20:** Methyl 2-((10*S*,13*S*)-10-acetamido-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00178]** Prepared in an analogous manner to **Intermediate 10** using **Intermediate 19** (0.18 g, 0.39 mmol), triethylamine (0.12 mL, 0.87 mmol), acetyl chloride (0.03 mL, 0.43 mmol) in DCM (5 mL) at RT for 30 min. Purified by flash chromatography (12 g silica gel, eluting 0 - 10% MeOH in DCM) to provide the title compound (96 mg). LCMS (Method 3): 1.59 min, 467.2 $[M+H]^+$.

**Intermediate 21:** Methyl (*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-methylpent-4-enamido)-3-(2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00179]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 4** (0.25 g, 0.78 mmol), (2*S*)-2-(*tert*-butoxycarbonylamino)-4-methyl-pent-4-enoic acid (0.18 g, 0.78 mmol, CAS 87325-47-1), DIPEA (0.27 mL, 1.56 mmol), HOBt (0.14 g, 0.93 mmol) and EDCI (0.18 g, 0.93 mmol) in DMF (5 mL) at RT for 4 h. Purified by flash chromatography (24 g silica gel, eluting 30-50% EtOAc in petroleum ether) to provide the title compound (0.24 g). LCMS (Method 3): 1.68 min, 497.1 $[M+H]^+$.

**Intermediate 22:** Methyl (*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-methylpent-4-enamido)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00180]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 21** (0.14 g, 0.28 mmol), $K_2CO_3$ (0.10 g, 0.71 mmol) and 5-bromopent-1-ene (0.07 mL, 0.57 mmol) in MeCN (20 mL) at reflux for 72 h. Purified by flash chromatography (24 g silica gel, eluting 30-50% EtOAc in petroleum ether) to provide the title compound (86 mg). LCMS (Method 3): 1.99 min, 565.3 $[M+H]^+$.

**Intermediate 23:** Methyl 2-((10*S*,13*S*)-10-((*tert*-butoxycarbonyl)amino)-2$^6$,8-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00181]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 22** (54 mg, 0.10 mmol) in DCE (45 mL) and Grubbs II (8.1 mg, 0.01 mmol) at 40 °C for 4 h. Quenched with ethyl vinyl ether (0.45 mL, 4.68 mmol). Purified by flash chromatography (24 g silica gel, eluting 30-50% EtOAc in petroleum ether) to provide the title compound (21 mg). LCMS (Method 4): 1.89 min, 537.1 $[M+H]^+$.

**Intermediate 24:** Methyl 2-((10*S*,13*S*)-10-((*tert*-butoxycarbonyl)amino)-2$^6$,8-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00182]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 23** (21 mg, 0.04 mmol) and 5% palladium on carbon (4 mg) in MeOH (5 mL) under a hydrogen atmosphere at RT for 3 h to provide the title compound (0.21 g). LCMS (Method 4): 1.92 min, 539.2 $[M+H]^+$.

**Intermediate 25:** Methyl 2-((10*S*,13*S*)-10-amino-2$^6$,8-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate hydrochloride

**[00183]** A suspension of **Intermediate 24** (21 g, 0.39 mmol) in 4 M HCl in 1,4-dioxane (2 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (18 mg). LCMS (Method 4): 1.62 min, 439.2 $[M+H]^+$.

**Intermediate 26:** Methyl 2-((10*S*,13*S*)-10-acetamido-2$^6$,8-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00184]** Prepared in an analogous manner to **Intermediate 10** using **Intermediate 25** (18 mg, 0.04 mmol), triethylamine (12 µL, 0.09 mmol), acetyl chloride (3 µL, 0.04 mmol) in DCM (5 mL) at RT for 30 min. Purified by flash chromatography (12 g silica gel, eluting 0 - 10% MeOH in DCM) to provide the title compound (19 mg). LCMS (Method 4): 2.08 min, 481.2 $[M+H]^+$.

**Intermediate 27:** Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5'-hydroxy-2'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00185]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 2** (1.0 g, 1.80 mmol), 3-bromo-4-methylphenol (0.31 g, 0.91 mmol, CAS 60710-39-6), $Na_2CO_3$ (0.80 g,

7.56 mmol) and $Pd(PPh_3)_4$ (95 mg, 0.05 mmol) in toluene (10.2 mL), ethanol (2 mL) and water (2 mL) at 85 °C for 16 h. Purified by flash chromatography (40 g silica gel, eluting 5 - 20% EtOAc in petroleum ether then 100% EtOAc) to provide the title compound (0.64 g). LCMS (Method 5): 1.48 min, 408.1 $[M+Na]^+$.

**Intermediate 28:** Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-methyl-5'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00186]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 27** (0.32 g, 0.83 mmol), $K_2CO_3$ (0.29 g, 2.08 mmol) and 5-bromopent-1-ene (0.20 mL, 1.66 mmol) in MeCN (20 mL) at reflux for 24 h to provide the title compound (0.37 g). LCMS (Method 5): 1.94 min, 452.4 $[M-H]^-$.

**Intermediate 29:** Methyl (*S*)-3-amino-3-(2'-methyl-5'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00187]** A suspension of **Intermediate 28** (0.27 g, 0.59 mmol) in 4 M HCl in 1,4-dioxane (5.0 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.26 g). LCMS (Method 5): 1.71 min, 354.3 $[M+H]^+$.

**Intermediate 30:** Methyl (*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enamido)-3-(2'-methyl-5'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00188]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 29** (0.23 g, 0.59 mmol), *N*-Boc-(S)-allylglycine (0.13 g, 0.59 mmol, CAS 90600-20-7), DIPEA (0.31 mL, 1.77 mmol), HOBt (0.10 g, 0.65 mmol) and EDCI (0.15 g, 0.77 mmol) in DMF (5 mL) at RT for 16 h. Purified by flash chromatography (24 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.14 g). LCMS (Method 4): 1.88 min, 551.4 $[M+H]^+$.

**Intermediate 31:** Methyl 2-((10*S*,13*S*)-10-((*tert*-butoxycarbonyl)amino)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1,2(1,3)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00189]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 30** (0.13 g, 0.24 mmol) in DCE (50 mL) and Grubbs II (20 mg, 0.02 mmol) in DCE (11 mL) at 40 °C for 5 h. Quenched with ethyl vinyl ether (3.0 mL, 31.3 mmol). Purified by flash chromatography (24 g silica gel, eluting 20 - 40% EtOAc in petroleum ether) to provide the title compound (93 mg). LCMS (Method 4): 1.69 and 1.73 min, 523.4 $[M+H]^+$.

**Intermediate 32:** Methyl 2-((10*S*,13*S*)-10-((*tert*-butoxycarbonyl)amino)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1,2(1,3)-dibenzenacyclotridecaphane-13-yl)acetate

**[00190]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 31** (93 mg, 0.13 mmol) and 5% palladium on carbon (14 mg) in MeOH (1.4 mL) under a hydrogen

atmosphere at RT for 2 h to provide the title compound (47 mg). LCMS (Method 4): 1.73 min, 525.4 $[M+H]^+$.

**Intermediate 33:** Methyl 2-((10*S*,13*S*)-10-amino-2$^6$-methyl-11-oxo-3-oxa-12-aza-1,2(1,3)-dibenzenacyclotridecaphane-13-yl)acetate hydrochloride

**[00191]** A solution of thionyl chloride (0.01 mL, 0.11 mmol) in MeOH (2 mL) was added to **Intermediate 32** (47 mg, 0.09 mmol) and the mixture was stirred at 60 °C for 4 h. The mixture was concentrated under reduced pressure to provide the title compound (38 mg). LCMS (Method 4): 1.42 min, 425.3 $[M+H]^+$.

**Intermediate 34:** Methyl 2-((10*S*,13*S*)-10-acetamido-2$^6$-methyl-11-oxo-3-oxa-12-aza-1,2(1,3)-dibenzenacyclotridecaphane-13-yl)acetate

**[00192]** Prepared in an analogous manner to **Intermediate 10** using **Intermediate 33** (38 mg, 0.09 mmol), triethylamine (2.8 µL, 0.20 mmol), acetyl chloride (7 µL, 0.10 mmol) in DCM (1 mL) at RT for 1 h to provide the title compound (37 mg). LCMS (Method 4): 1.44 min, 467.3 $[M+H]^+$.

**Intermediate 35:** Methyl (*S*)-3-(2'-(allyloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-methylpent-4-enamido)propanoate

**[00193]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 21** (0.14 g, 0.28 mmol), $K_2CO_3$ (0.10 g, 0.71 mmol) and allyl bromide (0.05 mL, 0.57 mmol) in MeCN (10 mL) at RT for 72 h. Purified by flash chromatography (24 g silica gel, eluting 30-50% EtOAc in petroleum ether) to provide the title compound (0.11 g). LCMS (Method 4): 1.90 min, 537.2 $[M+H]^+$.

**Intermediate 36:** Methyl 2-((8*S*,11*S*)-8-((*tert*-butoxycarbonyl)amino)-2$^6$,6-dimethyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphan-5-en-11-yl)acetate

**[00194]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 35** (0.11 g, 0.20 mmol) in DCE (98 mL) and Grubbs II (17 mg, 0.02 mmol) at 40 °C for 4 h. Purified by flash chromatography (24 g silica gel, eluting 30-50% EtOAc in petroleum ether) to provide the title compound (50 mg). LCMS (Method 4): 1.77 min, 509.0 $[M+H]^+$.

**Intermediate 37:** Methyl 2-((8*S*,11*S*)-8-((*tert*-butoxycarbonyl)amino)-2$^6$,6-dimethyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetate

**[00195]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 36** (50 mg, 0.10 mmol) and 5% palladium on carbon (11 mg) in MeOH (5 mL) under a hydrogen atmosphere at RT for 4 h to provide the title compound (46 mg). LCMS (Method 4): 1.77 min, 511.3 $[M+H]^+$.

**Intermediate 38:** Methyl 2-((8*S*,11*S*)-8-amino-2$^6$,6-dimethyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetate hydrochloride

**[00196]** A suspension of **Intermediate 37** (46 mg, 0.09 mmol) in 4 M HCl in 1,4-dioxane (2.0 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (40 mg). LCMS (Method 4): 1.50 min, 411.2 $[M+H]^+$.

**Intermediate 39:** Methyl 2-((8*S*,11*S*)-8-acetamido-2$^6$,6-dimethyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetate

**[00197]** Prepared in an analogous manner to **Intermediate 10** using **Intermediate 38** (40 mg, 0.09 mmol), triethylamine (2.7 µL, 0.20 mmol), acetyl chloride (7 µL, 0.10 mmol) in DCM (10 mL) at RT for 30 min. Purified by flash chromatography (12 g silica gel, eluting 0 - 10% MeOH in DCM) to provide the title compound (30 mg). LCMS (Method 4): 1.84 min, 453.2 $[M+H]^+$.

**Intermediate 40:** Methyl (*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)pent-4-enamido)-3-(2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00198]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 4** (0.17 g, 0.52 mmol), *N*-Boc-*N*-Methyl-(*S*)-allylglycine (0.12 g, 0.52 mmol, CAS 136092-76-7), DIPEA (0.18 mL, 1.04 mmol), HOBt (95 mg, 0.62 mmol) and EDCI (0.12 g, 0.62 mmol) in DMF (2 mL) at RT for 4 h, to provide the title compound (0.18 g). LCMS (Method 3): 1.73 min, 497.2 $[M+H]^+$.

**Intermediate 41:** Methyl (*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)pent-4-enamido)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00199]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 40** (0.18 g, 0.37 mmol), $K_2CO_3$ (0.13 g, 0.91 mmol) and 5-bromopent-1-ene (0.09 mL, 0.73 mmol) in MeCN (20 mL) at reflux for 16 h. Purified by flash chromatography (24 g silica gel, eluting 30 - 50% EtOAc in petroleum ether) to provide the title compound (0.12 g). LCMS (Method 4): 2.04 min, 565.3 $[M+H]^+$.

**Intermediate 42:** Methyl 2-((10*S*,13*S*)-10-((*tert*-butoxycarbonyl)(methyl)amino)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00200]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 41** (0.10 g, 0.17 mmol) in DCE (85 mL) and Grubbs II (14 mg, 0.17 mmol) at 40 °C for 4 h. Purified by flash chromatography (12 g XTYPE cartridge, eluting 10-40% EtOAc in petroleum ether) to provide the title compound (91 mg). LCMS (Method 4): 1.90 min, 537.3 $[M+H]^+$.

**Intermediate 43:** Methyl 2-((10*S*,13*S*)-10-((*tert*-butoxycarbonyl)(methyl)amino)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00201]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 42** (91 mg, 0.17 mmol) and 5% palladium on carbon (18 mg) in MeOH (10 mL) under a hydrogen atmosphere at RT for 3 h to provide the title compound (90 mg). LCMS (Method 4): 1.94 min, 539.3 $[M+H]^+$.

**Intermediate 44:** Methyl 2-((10*S*,13*S*)-2$^6$-methyl-10-(methylamino)-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate hydrochloride

**[00202]** A suspension of **Intermediate 43** (90 mg, 0.17 mmol) in 4 M HCl in 1,4-dioxane (3.0 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (79 mg). LCMS (Method 4): 1.48 min, 439.4 $[M+H]^+$.

**Intermediate 45:** Methyl 2-((10*S*,13*S*)-2$^6$-methyl-10-(*N*-methylacetamido)-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00203]** Prepared in an analogous manner to **Intermediate 10** using **Intermediate 44** (79 mg, 0.17 mmol), triethylamine (0.05 mL, 0.37 mmol), acetyl chloride (13 µL, 0.18 mmol) in DCM (5 mL) at RT for 30 min, to provide the title compound (80 mg). LCMS (Method 4): 1.56 min, 481.4 $[M+H]^+$.

**Intermediate 46:** Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-methyl-6'-vinyl-[1,1'-biphenyl]-3-yl)propanoate

**[00204]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 2** (1.1 g, 2.58 mmol), 2-bromo-1-methyl-3-vinylbenzene (0.59 g, 2.83 mmol, CAS 1835-81-0), $K_2CO_3$ (0.71 g, 5.16 mmol) and $Pd(dppf)Cl_2$ (0.11 g, 0.15 mmol) in 1,4-dioxane (19 mL), and water (6.4 mL) at 90 °C for 3 h. Purified by flash chromatography (40 g silica gel, eluting 100% DCM) to provide the title compound (0.76 g). LCMS (Method 4): 1.83 min, 418.3 $[M+Na]^+$.

**Intermediate 47:** Methyl (*S*)-3-amino-3-(2'-methyl-6'-vinyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00205]** A suspension of **Intermediate 46** (0.76 g, 1.69 mmol) in 4 M HCl in 1,4-dioxane (10 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.56 g). LCMS (Method 4): 1.65 min, 296.0 $[M+H]^+$.

**Intermediate 48:** Methyl (*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)non-8-enamido)-3-(2'-methyl-6'-vinyl-[1,1'-biphenyl]-3-yl)propanoate

**[00206]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 47** (0.21 g, 0.62 mmol), methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)non-8-enoate (0.18 g, 0.62 mmol, CAS 2375587-63-4), DIPEA (0.32 mL, 1.86 mmol), HOBt (92 mg, 0.68 mmol) and EDCI (0.15 g, 0.81 mmol) in DMF (18 mL) at RT for 4 h. Purified by flash chromatography (40 g silica gel,

eluting 0-10% EtOAc in DCM) to provide the title compound (0.10 g). LCMS (Method 5): 2.14 min, 463.2 $[M\text{-}Boc+H]^+$.

**Intermediate 49:** Methyl 2-((3*S*,6*S*)-6-((*tert*-butoxycarbonyl)(methyl)amino)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-12-en-3-yl)acetate

**[00207]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 48** (0.20 g, 0.32 mmol) in DCE (15 mL) and Grubbs II (27 mg, 0.04 mmol) at 60 °C for 16 h, quenching with ethyl vinyl ether (3.04 mL, 31.7 mmol). Purified by flash chromatography (silica gel, eluting 5% EtOAc in DCM) to provide the title compound (0.11 g). LCMS (Method 4): 1.98 min, 535.5 $[M+H]^+$.

**Intermediate 50:** Methyl 2-((3*S*,6*S*)-6-((*tert*-butoxycarbonyl)(methyl)amino)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00208]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 49** (91 mg, 0.17 mmol) and 5% palladium on carbon (18 mg) in MeOH (10 mL) under a hydrogen atmosphere at RT for 3 h to provide the title compound (90 mg). LCMS (Method 4): 1.94 min, 537.2 $[M+H]^+$.

**Intermediate 51:** Methyl 2-((3*S*,6*S*)-1$^6$-methyl-6-(methylamino)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate hydrochloride

**[00209]** A suspension of **Intermediate 50** (91 mg, 0.17 mmol) in 4 M HCl in 1,4-dioxane (1.5 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (79 mg). LCMS (Method 4): 1.66 min, 437.5 $[M+H]^+$.

**Intermediate 52:** Methyl 2-((3*S*,6*S*)-1$^6$-methyl-6-(*N*-methylacetamido)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00210]** Prepared in an analogous manner to **Intermediate 10** using **Intermediate 51** (79 mg, 0.17 mmol), triethylamine (0.05 mL, 0.37 mmol), acetyl chloride (13 µL, 0.18 mmol) in DCM (1.7 mL) at RT for 2 h, to provide the title compound (77 mg). LCMS (Method 4): 1.83 min, 479.3 $[M+H]^+$.

**Intermediate 53:** Methyl (*S*)-3-(2'-(but-3-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00211]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 3** (1.80 g, 4.67 mmol), $K_2CO_3$ (1.63 g, 11.7 mmol) and 4-bromobut-1-ene (0.96 mL, 9.34 mmol) in MeCN (41 mL) at reflux for 16 h. Purified by flash chromatography (25 g XTYPE cartridge, eluting 0 - 50% EtOAc in petroleum ether) to provide the title compound (1.0 g). LCMS (Method 3): 1.93 min, 462.2 $[M+Na]^+$.

**Intermediate 54:** Methyl (*S*)-3-amino-3-(2'-(but-3-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00212]** A suspension of **Intermediate 53** (1.0 g, 2.28 mmol) in 4 M HCl in 1,4-dioxane (53 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.85 g). LCMS (Method 3): 1.19 min, 340.3 $[M+H]^+$.

**Intermediate 55:** Methyl (*S*)-3-(2'-(but-3-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxyhex-5-enamido)propanoate

**[00213]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 54** (1.0 g, 2.66 mmol), (2*R*)-2-hydroxyhex-5-enoic acid (0.41 g, 2.66 mmol, CAS 612825-60-2), DIPEA (1.39 mL, 7.98 mmol), HOBt (0.36 g, 2.66 mmol) and EDCI (0.51 g, 2.66 mmol) in MeCN (27 mL) at RT for 5 h. Purified by flash chromatography (25 g silica gel, eluting 30-100% EtOAc in petroleum ether) to provide the title compound (0.80 g). LCMS (Method 3): 1.68 min, 452.4 $[M+H]^+$.

**Intermediate 56:** Methyl (*S*)-3-(2'-(but-3-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)hex-5-enamido)propanoate

**[00214]** To a solution of **Intermediate 55** (0.80 g, 1.77 mmol) and triethylamine (0.49 mL, 3.54 mmol) in DCM (125 mL) was added methanesulfonyl chloride (0.21 mL, 2.66 mmol) and the mixture stirred at RT for 1 h. The mixture was washed with 2 M aqueous HCl, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure, to provide the title compound (0.94 g). LCMS (Method 3): 1.82 min, 530.1 $[M+H]^+$.

**Intermediate 57:** Methyl (*S*)-3-(2'-(but-3-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(2-oxopyridin-1(2*H*)-yl)hex-5-enamido)propanoate

**[00215]** To a solution of **Intermediate 56** (0.47 g, 0.89 mmol) and pyridin-2-ol (0.19 g, 1.95 mmol) in MeCN (1 mL) was added $K_2CO_3$ (0.37 g, 2.66 mmol) and the mixture stirred at 95 °C for 1 h. Additional $K_2CO_3$ (0.37 g, 2.66 mmol) was added, and the mixture stirred at 95 °C for 2 h. The mixture was cooled, filtered and the filtrate concentrated under reduced pressure. The crude product was purified by flash chromatography (24 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (0.33 g). LCMS (Method 2): 2.28 min, 551.3 $[M+Na]^+$.

**Intermediate 58:** Methyl 2-((10*S*,13*S*)-2$^6$-methyl-11-oxo-10-(2-oxopiperidin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-6-en-13-yl)acetate

**[00216]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 57** (0.33 g, 0.62 mmol) in DCE (31 mL) and Grubbs II (53 mg, 0.06 mmol) at 40 °C for 1 h, quenching with ethyl vinyl ether (0.06 mL, 0.62 mmol). Purified by flash chromatography (25 g silica gel,

eluting 0-100% EtOAc in petroleum ether) to provide the title compound (0.10 g). LCMS (Method 4): 1.66 min, 501.2 $[M+H]^+$.

**Intermediate 59:** Methyl 2-((10*S*,13*S*)-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00217]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 58** (0.10 g, 0.20 mmol) and 5% palladium on carbon (21 mg) in MeOH (5 mL) under a hydrogen atmosphere at RT for 2 h to provide the title compound (75 mg). LCMS (Method 3): 1.70 min, 503.2 $[M+H]^+$.

**Intermediate 60:** Methyl (*S*)-3-(2'-(but-3-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)hex-5-enamido)propanoate

**[00218]** Prepared in an analogous manner to **Intermediate 57** using **Intermediate 56** (0.20 g, 0.38 mmol), 4-(trifluoromethyl)pyridin-2-ol (0.14 g, 0.83 mmol) and $K_2CO_3$ (0.16 g, 1.13 mmol) in MeCN (1 mL) at 95 °C for 2 h. Purified by flash chromatography (24 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (0.20 g). LCMS (Method 3): 1.94 min, 597.3 $[M+H]^+$.

**Intermediate 61:** Methyl 2-((10*S*,13*S*)-2$^6$-methyl-11-oxo-10-(2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-6-en-13-yl)acetate

**[00219]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 60** (0.20 g, 0.34 mmol) in DCE (17 mL) and Grubbs II (28 mg, 0.03 mmol) at 40 °C for 1 h. Purified by flash chromatography (24 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (0.10 g). LCMS (Method 3): 1.84 min, 569.2 $[M+H]^+$.

**Intermediate 62:** Methyl 2-((10*S*,13*S*)-2$^6$-methyl-11-oxo-10-(2-oxo-4-(trifluoromethyl)-pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00220]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 61** (0.10 g, 0.20 mmol) and 5% palladium on carbon (10 mg) in MeOH (5 mL) under a hydrogen atmosphere at RT for 1 h to provide the title compound (0.10 g). LCMS (Method 3): 1.87 min, 571.2 $[M+H]^+$.

**Intermediate 63:** Methyl (*S*)-3-(2'-(but-3-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00221]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 54** (0.10 g, 0.27 mmol), (2*R*)-2-hydroxypent-4-enoic acid (31 mg, 0.27 mmol, CAS 413622-10-3), DIPEA (0.14 mL, 0.80 mmol), HOBt (36 mg, 0.27 mmol) and EDCI (56 mg, 0.27 mmol) in MeCN (10

mL) at RT for 5 h, to provide the title compound (0.11 g). LCMS (Method 3): 1.72 min, 438.2 $[M+H]^+$.

**Intermediate 64:** Methyl (*S*)-3-(2'-(but-3-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00222]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 63** (0.11 g, 0.25 mmol), triethylamine (35 µL, 0.50 mmol) and methanesulfonyl chloride (29 µL, 0.38 mmol) in DCM (5 mL) at RT for 10 min. Purified by flash chromatography (12 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (75 mg). LCMS (Method 3): 1.78 min, 516.2 $[M+H]^+$.

**Intermediate 65:** Methyl (*S*)-3-(2'-(but-3-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00223]** To a solution of pyridin-2-ol (17 mg, 0.18 mmol) in THF (3 mL) was added sodium hydride (60% dispersion in mineral oil, 7 mg, 0.18 mmol) at RT. After 5 min, **Intermediate 64** (75 mg, 0.15 mmol) was added as a solution in THF (3 mL) and the mixture was stirred at reflux for 18 h. The mixture was cooled and diluted with EtOAc, washed with water, dried over $Na_2SO_4$, filtered and the filtrate concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (30 mg). LCMS (Method 3): 2.23 min, 515.2 $[M+H]^+$.

**Intermediate 66:** Methyl 2-((9*S*,12*S*)-$2^6$-methyl-10-oxo-9-(2-oxopyridin-1(2*H*)-yl)-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphan-6-en-12-yl)acetate

**[00224]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 65** (45 mg, 0.09 mmol) in DCE (4.4 mL) and Grubbs II (7.4 mg, 8.7 µmol) at 40 °C for 2 h. Purified by flash chromatography (14 g XTYPE cartridge, eluting 100% EtOAc) to provide the title compound (5 mg). LCMS (Method 3): 1.50 min, 487.4 $[M+H]^+$.

**Intermediate 67:** Methyl 2-((9*S*,12*S*)-$2^6$-methyl-10-oxo-9-(2-oxopiperidin-1-yl)-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetate

**[00225]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 66** (5 mg, 0.01 mmol) and platinum oxide (1 mg, 4.4 µmol) in MeOH (5 mL) under a hydrogen atmosphere at RT for 2 h to provide the title compound (5 mg). LCMS (Method 3): 1.66 min, 493.3 $[M+H]^+$.

**Intermediate 68:** Methyl 2-((10*R*,13*S*)-10-hydroxy-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-6-en-13-yl)acetate

**[00226]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 55** (550 mg, 1.22 mmol) in DCE (58 mL) and Grubbs II (0.10 g, 0.12 mmol) at 40 °C for 4 h. Purified by flash chromatography (40 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (0.32 g). LCMS (Method 3): 1.58 min, 424.3 $[M+H]^+$.

**Intermediate 69:** Methyl 2-((10*R*,13*S*)-$2^6$-methyl-10-((methylsulfonyl)oxy)-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-6-en-13-yl)acetate

**[00227]** To a solution of **Intermediate 68** (0.32 g, 0.55 mmol) and triethylamine (0.09 mL, 0.64 mmol) in DCM (5 mL) was added methanesulfonyl chloride (0.04 mL, 0.48 mmol) and the mixture stirred at RT for 1 h. The mixture was concentrated under reduced pressure and the crude product purified by flash chromatography (40 g silica gel, eluting 20-100% EtOAc in petroleum ether) to provide the title compound (0.33 g). LCMS (Method 3): 1.68 min, 502.1 $[M+H]^+$.

**Intermediate 70:** Methyl 2-((10*S*,13*S*)-10-azido-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-6-en-13-yl)acetate

**[00228]** To a solution of **Intermediate 69** (0.32 g, 0.47 mmol) in DMF (6.4 mL) was added sodium azide (34 mg, 0.52 mmol) and the mixture stirred at 90 °C for 72 h. The mixture was diluted with EtOAc and water. The aqueous was extracted with EtOAc then the organics washed with brine and concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g silica gel, eluting 20-50% EtOAc in petroleum ether) to provide the title compound (0.12 g). LCMS (Method 4): 1.69 and 1.77 min, 449.1 $[M+H]^+$.

**Intermediate 71:** Methyl 2-((10*S*,13*S*)-10-amino-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00229]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 70** (0.12 g, 0.24 mmol) and 10% palladium on carbon (11 mg) in MeOH (8 mL) under a hydrogen atmosphere at RT for 2 h to provide the title compound (52 mg). LCMS (Method 4): 1.27 min, 425.2 $[M+H]^+$.

**Intermediate 72:** 4-(((10*S*,13*S*)-13-(2-Methoxy-2-oxoethyl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-10-yl)amino)butanoic acid

**[00230]** To a solution of **Intermediate 71** (47 mg, 0.11 mmol) and succinic semialdehyde (83 mg, 0.12 mmol, CAS 629-29-5) in DCE (2 mL) and AcOH (7 µL, 0.12 mmol) was added STAB (26 mg, 0.12 mmol) and the mixture stirred at RT for 15 h. The mixture was diluted with water (2 mL) and extracted with 10% MeOH in DCM. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash

chromatography (12 g silica gel, eluting 50-100% EtOAc in petroleum ether then 20% MeOH in DCM) to provide the title compound (12 mg). LCMS (Method 4): 1.63 min, 511.2 $[M+H]^+$.

**Intermediate 73:** Methyl (*S*)-3-(2'-(allyloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00231]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 3** (1.0 g, 2.59 mmol), $K_2CO_3$ (0.39 g, 2.85 mmol) and allyl bromide (0.25 mL, 2.85 mmol) in MeCN (50 mL) at 50 °C for 16 h to provide the title compound (1.1 g). LCMS (Method 4): 1.86 min, 448.1 $[M+Na]^+$.

**Intermediate 74:** Methyl (*S*)-3-(2'-(allyloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-aminopropanoate hydrochloride

**[00232]** A suspension of **Intermediate 73** (1.1 g, 2.58 mmol) in 4 M HCl in 1,4-dioxane (50 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.93 g). LCMS (Method 3): 1.22 min, 326.1 $[M+H]^+$.

**Intermediate 75:** Methyl (*S*)-3-(2'-(allyloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00233]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 74** (0.94 g, 2.87 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.33 g, 2.87 mmol, CAS 413622-10-3), DIPEA (1.50 mL, 8.62 mmol), HOBt (0.43 g, 3.16 mmol) and EDCI (0.61 g, 3.16 mmol) in MeCN (20 mL) at RT for 16 h. Purified by flash chromatography (24 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (0.13 g). LCMS (Method 3): 1.63 min, 424.2 $[M+H]^+$.

**Intermediate 76:** Methyl (*S*)-3-(2'-(allyloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00234]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 75** (0.50 g, 1.18 mmol), triethylamine (0.17 mL, 1.18 mmol) and methanesulfonyl chloride (0.09 mL, 1.18 mmol) in DCM (10 mL) at RT for 10 min. Purified by flash chromatography (24 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.45 g). LCMS (Method 3): 1.62 min, 524.3 $[M+Na]^+$.

**Intermediate 77:** Methyl (*S*)-3-(2'-(allyloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00235]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 76** (0.45 g, 0.90 mmol), pyridin-2-ol (0.10 g, 1.08 mmol) and sodium hydride (60% dispersion in mineral oil, 43 mg, 1.08 mmol) in THF (10 mL) at 80 °C for 16 h. Purified by flash chromatography (12

g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (0.25 g). LCMS (Method 3): 1.71 min, 501.2 $[M+H]^+$.

**Intermediate 78:** Methyl 2-((8*S*,11*S*)-2$^6$-methyl-9-oxo-8-(2-oxopyridin-1(2*H*)-yl)-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphan-5-en-11-yl)acetate

**[00236]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 77** (0.23 g, 0.45 mmol) in DCE (23 mL) and Grubbs II (38 mg, 0.05 mmol) at 40 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (0.20 g). LCMS (Method 3): 1.56 min, 473.2 $[M+H]^+$.

**Intermediate 79:** Methyl 2-((8*S*,11*S*)-2$^6$-methyl-9-oxo-8-(2-oxopyridin-1(2*H*)-yl)-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetate

**[00237]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 78** (0.20 g, 0.42 mmol) and 10% palladium on carbon (12 mg) in MeOH (5 mL) and THF (5 mL) under a hydrogen atmosphere at RT for 2 h. Purified by flash chromatography (40 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (0.10 g). LCMS (Method 3): 1.57 min, 475.2 $[M+H]^+$.

**Intermediate 80:** Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-fluoro-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00238]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 2** (0.80 g, 1.68 mmol), 2-bromo-5-fluoro-3-methylphenol (0.41 g, 1.68 mmol, CAS 1807192-21-7), $Na_2CO_3$ (0.53 g, 5.03 mmol) and $Pd(PPh_3)_4$ (0.09 g, 0.08 mmol) in toluene (14.8 mL) ethanol (3.1 mL) and water (3.1 mL) at 85 °C for 8 h. Purified by flash chromatography (40 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.42 g). LCMS (Method 3): 1.66 min, 426.1 $[M+Na]^+$.

**Intermediate 81:** Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00239]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 80** (0.42 g, 1.04 mmol), $K_2CO_3$ (0.22 g, 1.56 mmol) and 5-bromopent-1-ene (0.19 mL, 1.56 mmol) in MeCN (20 mL) at reflux for 16 h. Purified by flash chromatography (12 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.35 g). LCMS (Method 6): 1.93 min, 494.4 $[M+Na]^+$.

**Intermediate 82:** Methyl (*S*)-3-amino-3-(4'-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00240]** A suspension of **Intermediate 81** (0.35 g, 0.74 mmol) in 4 M HCl in 1,4-dioxane (5 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.30 g). LCMS (Method 3): 1.54 min, 372.2 $[M+H]^+$.

**Intermediate 83:** Methyl (*S*)-3-(4'-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00241]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 82** (0.32 g, 0.80 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.14 g, 1.19 mmol, CAS 413622-10-3), DIPEA (0.42 mL, 2.38 mmol), HOBt (0.12 g, 0.88 mmol) and EDCI (0.12 g, 1.03 mmol) in MeCN (20 mL) at RT for 16 h, to provide the title compound (0.13 g). LCMS (Method 7): 2.29 min, 470.2 $[M+H]^+$.

**Intermediate 84:** Methyl (*S*)-3-(4'-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00242]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 83** (0.35 g, 0.75 mmol), triethylamine (0.16 mL, 1.12 mmol) and methanesulfonyl chloride (0.09 mL, 1.12 mmol) in DCM (10 mL) at RT for 10 min. Purified by flash chromatography (24 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.20 g). LCMS (Method 3): 1.86 min, 548.3 $[M+H]^+$.

**Intermediate 85:** Methyl (*S*)-3-(4'-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00243]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 84** (0.20 g, 0.37 mmol), pyridin-2-ol (42 mg, 0.44 mmol) and sodium hydride (60% dispersion in mineral oil, 17.5 mg, 0.44 mmol) in THF (10 mL) at 80 °C for 16 h. Purified by flash chromatography (12 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (35 mg). LCMS (Method 3): 1.84 min, 547.2 $[M+H]^+$.

**Intermediate 86:** Methyl 2-((10*S*,13*S*)-$2^4$-fluoro-$2^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00244]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 85** (35 mg, 0.06 mmol) in DCE (3.2 mL) and Grubbs II (5.4 mg, 6.4 µmol) at 40 °C for 0.5 h. Purified by flash chromatography (4 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (20 mg). LCMS (Method 3): 1.71 min, 519.2 $[M+H]^+$.

**Intermediate 87:** Methyl 2-((10*S*,13*S*)-$2^4$-fluoro-$2^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00245]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 86** (20 mg, 0.04 mmol) and 10% palladium on carbon (0.4 mg) in MeOH (1 mL) and THF (1 mL) under a hydrogen atmosphere at RT for 8 h, to provide the title compound (20 mg). LCMS (Method 3): 1.75 min, 521.3 $[M+H]^+$.

**Intermediate 88:** Methyl (*S*)-3-(2'-(but-3-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-fluoro-2-oxopyridin-1(2*H*)-yl)hex-5-enamido)propanoate

**[00246]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 56** (0.25 g, 0.47 mmol), 5-fluoropyridin-2-ol (64 mg, 0.57 mmol, CAS 51173-05-8) and sodium hydride (60% dispersion in mineral oil, 23 mg, 0.57 mmol) in THF (10 mL) at 80 °C for 16 h. Purified by flash chromatography (40 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (25 mg). LCMS (Method 7): 2.51 min, 547.2 $[M+H]^+$.

**Intermediate 89:** Methyl 2-((10*S*,13*S*)-10-(5-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-6-en-13-yl)acetate

**[00247]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 88** (25 mg, 0.05 mmol) in DCE (5 mL) and Grubbs II (7.8 mg, 9.1 µmol) at 40 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 30-100% EtOAc in petroleum ether) to provide the title compound (14 mg). LCMS (Method 6): 1.61 min, 519.2 $[M+H]^+$.

**Intermediate 90:** Methyl 2-((10*S*,13*S*)-10-(5-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00248]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 89** (14 mg, 0.02 mmol) and 10% palladium on carbon (0.2 mg) in MeOH (1.5 mL) under a hydrogen atmosphere at RT for 24 h, to provide the title compound (10 mg). LCMS (Method 3): 1.77 min, 521.3 $[M+H]^+$.

**Intermediate 91:** Methyl 3-(5-bromopyridin-3-yl)-3-((*tert*-butoxycarbonyl)amino)-propanoate

**[00249]** To a solution of 5-bromopyridine-3-carbaldehyde (20 g, 0.11 mol, CAS 113118-81-3) and malonic acid (11.2 g, 108 mmol) in ethanol (100 mL) was added ammonium acetate (8.29 g, 108 mmol) and the mixture stirred at 75 °C for 24 h. The mixture was cooled to RT and the solids filtered, washing with ice cold ethanol, IPA and petroleum ether. The solid was dissolved in 1 M HCl in methanol (400 mL) and stirred at 65 °C for 24 h. The mixture was concentrated under reduced pressure then suspended in DCM (200 mL) followed by the addition of triethylamine (45 mL, 323 mmol) and Boc anhydride (23.5 g, 0.11 mol) and stirred at RT for 6 h. The mixture was washed with water (2 mL) and brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by dry flash

chromatography (silica gel, eluting 5-35% EtOAc in petroleum ether) to provide the title compound (14.7 g). LCMS (Method 4): 1.42 min, 359.1 $[M+H]^+$.

**Intermediate 92:** Methyl 3-((*tert*-butoxycarbonyl)amino)-3-(5-(2-hydroxy-6-methylphenyl)pyridin-3-yl)propanoate

**[00250]** A solution of **Intermediate 91** (4.0 g, 11.1 mmol) and bis(pinacolato)diboron (4.24 g, 16.7 mmol) in 1,4-dioxane (60 mL) was degassed with nitrogen. To the solution was then added potassium acetate (2.73 g, 27.8 mmol) followed by $Pd(dppf)Cl_2$ (0.41 g, 0.56 mmol) and the reaction mixture stirred at 100 °C for 1 h. The mixture was cooled then a degassed solution of $Na_2CO_3$ (2.36 g, 22.3 mmol) in water (40 mL) was added followed by 2-bromo-3-methylphenol (3.12 g, 16.7 mmol) and the mixture was stirred at 95 °C for 2 h. The mixture was cooled and filtered through Celite®, washing with EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (120 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (2.6 g). LCMS (Method 6): 1.16 min, 387.4 $[M+H]^+$.

**Intermediate 93:** Methyl 3-((*tert*-butoxycarbonyl)amino)-3-(5-(2-methyl-6-(pent-4-en-1-yloxy)phenyl)pyridin-3-yl)propanoate

**[00251]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 92** (2.60 g, 6.32 mmol), $K_2CO_3$ (1.75 g, 12.7 mmol) and 5-bromopent-1-ene (0.90 mL, 7.59 mmol) in MeCN (35 mL) at reflux for 6 h. Purified by flash chromatography (80 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (2.00 g). LCMS (Method 3): 1.77 min, 455.2 $[M+H]^+$.

**Intermediate 94:** Methyl 3-amino-3-(5-(2-methyl-6-(pent-4-en-1-yloxy)phenyl)pyridin-3-yl)propanoate hydrochloride

**[00252]** A suspension of **Intermediate 93** (2.00 g, 4.40 mmol) in 4 M HCl in 1,4-dioxane (62 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (1.90 g). LCMS (Method 6): 1.42 min, 355.4 $[M+H]^+$.

**Intermediate 95:** Methyl (*S*)-3-((*R*)-2-hydroxypent-4-enamido)-3-(5-(2-methyl-6-(pent-4-en-1-yloxy)phenyl)pyridin-3-yl)propanoate

**[00253]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 94** (2.0 g, 5.12 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.59 g, 5.12 mmol, CAS 413622-10-3), DIPEA (0.89 mL, 5.12 mmol), HOBt (0.69 g, 5.12 mmol) and EDCI (1.08 g, 5.63 mmol) in MeCN (20 mL) at RT for 2 h. Purified by flash chromatography (80 g silica gel, eluting 50-100% EtOAc

in petroleum ether) to provide the title compound (0.48 g) as the second diastereomer eluted. LCMS (Method 4): 1.55 min, 453.2 $[M+H]^+$.

**Intermediate 96:** Methyl (*S*)-3-(5-(2-methyl-6-(pent-4-en-1-yloxy)phenyl)pyridin-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00254]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 95** (0.48 g, 1.06 mmol), triethylamine (0.30 mL, 2.12 mmol) and methanesulfonyl chloride (0.12 mL, 1.59 mmol) in DCM (20 mL) at RT for 10 min. Purified by flash chromatography (40 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.38 g). LCMS (Method 3): 1.59 min, 531.2 $[M+H]^+$.

**Intermediate 97:** Methyl (*S*)-3-(5-(2-methyl-6-(pent-4-en-1-yloxy)phenyl)pyridin-3-yl)-3-((*S*)-2-(2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00255]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 96** (0.38 g, 0.71 mmol), pyridin-2-ol (81 mg, 0.85 mmol) and sodium hydride (60% dispersion in mineral oil, 34 mg, 0.85 mmol) in THF (20 mL) at 80 °C for 16 h. Purified by flash chromatography (12 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (0.12 g). LCMS (Method 3): 1.54 min, 530.3 $[M+H]^+$.

**Intermediate 98:** Methyl 2-((10*S*,13*S*)-$2^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphan-7-en-13-yl)acetate

**[00256]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 97** (0.12 g, 0.23 mmol) in DCE (9 mL) and Grubbs II (38 mg, 0.05 mmol) at 40 °C for 24 h. Additional Grubbs II (19 mg, 0.02 mmol) was added and heated at 40 °C for 15 h. Purified by flash chromatography (40 g silica gel, eluting 30-100% EtOAc in petroleum ether) to provide the title compound (60 mg). LCMS (Method 3): 1.35 min, 502.2 $[M+H]^+$.

**Intermediate 99:** Methyl 2-((10*S*,13*S*)-$2^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetate

**[00257]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 98** (43 mg, 0.09 mmol) and platinum oxide (1.9 mg) in MeOH (1.5 mL) under a hydrogen atmosphere at RT for 3.5 h, to provide the title compound (35 mg). LCMS (Method 3): 1.40 min, 504.2 $[M+H]^+$ - note also contaminated with lactam, 508.3 in LCMS.

**Intermediate 100:** 2-((10*S*,13*S*)-$2^6$-Methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetic acid

**[00258]** A mixture of **Intermediate 99** (53 mg, 0.10 mmol) was dissolved in MeOH (2 mL), THF (1 mL) and water (1 mL) then lithium hydroxide (2.5 mg, 0.10 mmol) was added and the

solution stirred at RT for 4 h. The solution was adjusted to pH 4 with 2 M aqueous HCl and then the mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (32 g C18, eluting 0-60% MeCN in 1% aqueous formic acid) to provide the title compound (12 mg), contaminated with lactam. LCMS (Method 3): 1.21 min, 490.1 $[M+H]^+$; 1.23 min, 494.2 $[M+H]^+$ lactam.

**Intermediate 101:** 5-(4-Fluoro-2-hydroxy-6-methylphenyl)nicotinaldehyde

**[00259]** Prepared in an analogous manner to **Intermediate 3** using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carbaldehyde (1.70 g, 7.29 mmol, CAS 848093-29-8), 2-bromo-5-fluoro-3-methylphenol (1.76 g, 7.29 mmol, CAS 1807192-21-7), $Na_2CO_3$ (2.32 g, 21.9 mmol) and $Pd(PPh_3)_4$ (0.38 g, 0.33 mmol) in toluene (52 mL), ethanol (13 mL) and water (13 mL) at 85 °C for 8 h. Purified by dry flash chromatography (silica gel, eluting 50% EtOAc in petroleum ether) to provide the title compound (1.37 g). LCMS (Method 3): 1.25 min, 232.0 $[M+H]^+$.

**Intermediate 102:** (*R*,*E*)-*N*-((5-(4-Fluoro-2-hydroxy-6-methylphenyl)pyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide

**[00260]** To a solution of **Intermediate 101** (1.37 g, 5.93 mmol) in THF (0.11 L) was added (*R*)-2-methylpropane-2-sulfinimide (0.79 g, 6.51 mmol, CAS 196929-78-9) and titanium ethoxide (1.38 g, 8.89 mmol) then the mixture was stirred at 60 °C for 2 h. The mixture was diluted with water and extracted into EtOAc. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g silica gel, eluting 50 – 100% EtOAc in petroleum ether) to provide the title compound (0.75 g). LCMS (Method 3): 1.48 min, 335.1 $[M+H]^+$.

**Intermediate 103:** (*R*,*E*)-*N*-((5-(4-Fluoro-2-methyl-6-(pent-4-en-1-yloxy)phenyl)pyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide

**[00261]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 102** (0.75 g, 2.24 mmol), $K_2CO_3$ (0.62 g, 4.49 mmol) and 5-bromopent-1-ene (0.53 mL, 4.49 mmol) in MeCN (22 mL) at reflux for 18 h. Extra $K_2CO_3$ (0.62 g, 4.49 mmol) and 5-bromopent-1-ene (0.53 mL, 4.49 mmol) was added and heating continued for 5 h. Purified by flash chromatography (24 g silica gel, eluting 0 - 50% EtOAc in petroleum ether) to provide the title compound (0.85 g). LCMS (Method 3): 1.90 min, 403.1 $[M+H]^+$.

**Intermediate 104:** Ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(5-(4-fluoro-2-methyl-6-(pent-4-en-1-yloxy)phenyl)pyridin-3-yl)propanoate

**[00262]** To a suspension of zinc (0.69 g, 10.6 mmol) in THF (15 mL) was added chlorotrimethylsilane (0.05 mL, 0.42 mmol) and stirred at 60 °C for 1 h. The mixture was cooled

to RT then ethyl bromoacetate (0.59 mL, 5.30 mmol) was added and the mixture placed in a sonic bath at 40 °C for 15 min. The mixture was cooled at 0 °C then a solution of **Intermediate 103** (0.85 g, 2.11 mmol) in THF (15 mL) was added then the mixture was stirred at RT for 1 h. The mixture was diluted with water and extracted into EtOAc. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (0.80 g). LCMS (Method 3): 1.69 min, 491.1 $[M+H]^+$.

**Intermediate 105:** Ethyl (*S*)-3-amino-3-(5-(4-fluoro-2-methyl-6-(pent-4-en-1-yloxy)phenyl)pyridin-3-yl)propanoate hydrochloride

**[00263]** To a suspension of **Intermediate 104** (0.80 g, 1.63 mmol) in DCM (1.1 mL) was added 4 M HCl in 1,4-dioxane (2.45 mL) and this was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.63 g). LCMS (Method 3): 1.31 min, 387.1 $[M+H]^+$.

**Intermediate 106:** Ethyl (*S*)-3-(5-(4-Fluoro-2-methyl-6-(pent-4-en-1-yloxy)phenyl)pyridin-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00264]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 105** (0.69 g, 1.63 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.28 g, 2.45 mmol, CAS 413622-10-3), DIPEA (0.85 mL, 4.89 mmol), HOBt (0.29 g, 2.12 mmol) and EDCI (0.34 g, 1.79 mmol) in MeCN (20 mL) at RT for 4 h, to provide the title compound (0.55 g) as the second diastereomer eluted. LCMS (Method 3): 1.57 min, 485.2 $[M+H]^+$.

**Intermediate 107:** Ethyl (*S*)-3-(5-(4-fluoro-2-methyl-6-(pent-4-en-1-yloxy)phenyl)pyridin-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00265]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 106** (0.55 g, 1.14 mmol), triethylamine (0.32 mL, 2.27 mmol) and methanesulfonyl chloride (0.13 mL, 1.48 mmol) in DCM (10 mL) at RT for 30 min. Purified by flash chromatography (24 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.52 g). LCMS (Method 6): 1.57 min, 563.5 $[M+H]^+$.

**Intermediate 108:** Ethyl (*S*)-3-(5-(4-fluoro-2-methyl-6-(pent-4-en-1-yloxy)phenyl)pyridin-3-yl)-3-((*S*)-2-(2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00266]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 107** (0.55 g, 0.98 mmol), pyridin-2-ol (0.11 g, 0.85 mmol) and sodium hydride (60% dispersion in mineral oil, 47 mg, 1.17 mmol) in THF (20 mL) at 80 °C for 10 h. Purified by flash chromatography (24 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (0.14 g). LCMS (Method 3): 1.62 min, 562.3 $[M+H]^+$.

**Intermediate 109:** Ethyl 2-((10*S*,13*S*)-2$^4$-fluoro-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphan-7-en-13-yl)acetate

**[00267]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 108** (0.13 g, 0.22 mmol) in DCE (9 mL) and Grubbs II (19 mg, 0.02 mmol) at 40 °C for 18 h. Additional Grubbs II (19 mg, 0.02 mmol) was added and heated at 40 °C for 24 h. Additional Grubbs II (19 mg, 0.02 mmol) was added and heated at 40 °C for 24 h. Additional Grubbs II (19 mg, 0.02 mmol) was added and heated at 40 °C for 24 h. Purified by flash chromatography (24 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (80 mg). LCMS (Method 3): 1.43 min, 534.2 $[M+H]^+$.

**Intermediate 110:** Ethyl 2-((10*S*,13*S*)-2$^4$-fluoro-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetate

**[00268]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 109** (80 mg, 0.15 mmol) and 10% palladium on carbon (10 mg) in MeOH (2 mL) under a hydrogen atmosphere at RT for 4 h, to provide the title compound (10 mg). LCMS (Method 6): 1.40 min, 536.5 $[M+H]^+$.

**Intermediate 111:** Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00269]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 3** (3.06 g, 6.91 mmol), $K_2CO_3$ (1.91 g, 13.8 mmol) and 5-bromopent-1-ene (0.92 mL, 13.8 mmol) in MeCN (38 mL) at reflux for 8 h. Extra $K_2CO_3$ (0.95 g, 6.91 mmol) and 5-bromopent-1-ene (0.82 mL, 6.91 mmol) was added and heating continued for 4 h. Extra $K_2CO_3$ (0.48 g, 3.45 mmol) and 5-bromopent-1-ene (0.41 mL, 3.45 mmol) was added and heating continued for 4 h. Purified by flash chromatography (120 g silica gel, eluting 0 - 30% EtOAc in petroleum ether) to provide the title compound (2.63 g). LCMS (Method 6): 1.92 min, 454.5 $[M+H]^+$.

**Intermediate 112:** Methyl (*S*)-3-amino-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00270]** A suspension of **Intermediate 111** (2.79 g, 5.79 mmol) in 4 M HCl in 1,4-dioxane (60 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (3.06 g). LCMS (Method 6): 1.20 min, 354.4 $[M+H]^+$.

**Intermediate 113:** Methyl (*S*)-3-((*R*)-2-hydroxypent-4-enamido)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00271]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 112** (2.15 g, 5.18 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.90 g, 7.77 mmol, CAS 413622-10-3), DIPEA (2.71 mL, 15.5 mmol), HOBt (0.77 g, 5.70 mmol) and EDCI (1.29 g, 6.74 mmol) in

MeCN (0.10 L) at RT for 18 h, to provide the title compound (3.98 g). LCMS (Method 6): 1.68 min, 452.4 $[M+H]^+$.

**Intermediate 114:** Methyl (*S*)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00272]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 113** (2.80 g, 6.20 mmol), triethylamine (1.72 mL, 12.4 mmol) and methanesulfonyl chloride (0.72 mL, 9.30 mmol) in DCM (20 mL) at RT for 2 h. Additional triethylamine (0.86 mL, 6.20 mmol) and methanesulfonyl chloride (0.48 mL, 6.20 mmol) were added and stirred at RT for 2 h. Additional triethylamine (0.86 mL, 6.20 mmol) and methanesulfonyl chloride (0.48 mL, 6.20 mmol) were added and stirred at RT for 18 h. Purified by flash chromatography (24 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (1.76 g). LCMS (Method 3): 1.83 min, 530.2 $[M+H]^+$.

**Intermediate 115:** Methyl (*S*)-3-((*S*)-2-(4-fluoro-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00273]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 114** (0.35 g, 0.66 mmol), 4-fluoro-1*H*-pyridin-2-one (92 mg, 0.79 mmol, CAS 96530-75-5) and sodium hydride (60% dispersion in mineral oil, 32 mg, 0.79 mmol) in THF (14 mL) at 80 °C for 18 h. Purified by flash chromatography (40 g silica gel, eluting 30-100% EtOAc in petroleum ether) and reverse phase chromatography (32 g C18, eluting 30-90% MeCN in 1% aqueous formic acid) to provide the title compound (16 mg). LCMS (Method 3): 1.76 min, 547.2 $[M+H]^+$.

**Intermediate 116:** Methyl 2-((10*S*,13*S*)-10-(4-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00274]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 115** (16 mg, 0.03 mmol) in DCE (3.3 mL) and Grubbs II (2.5 mg, 3 μmol) at RT for 5 h. Purified by flash chromatography (4 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (10 mg). LCMS (Method 3): 1.59 min, 519.2 $[M+H]^+$.

**Intermediate 117:** Methyl 2-((10*S*,13*S*)-10-(4-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00275]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 116** (10 mg, 0.02 mmol) and 10% palladium on carbon (0.2 mg) in MeOH (1.5 mL) under a hydrogen atmosphere at RT for 5 h, to provide the title compound (10 mg). LCMS (Method 3): 1.63 min, 521.3 $[M+H]^+$.

**Intermediate 118:** Methyl (*S*)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(2-oxo-5-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00276]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 114** (0.20 g, 0.38 mmol), 5-(trifluoromethyl)-1*H*-pyridin-2-one (74 mg, 0.45 mmol, CAS 33252-63-0) and $K_2CO_3$ (52 mg, 0.38 mmol) in THF (20 mL) at 80 °C for 2 h. Additional $K_2CO_3$ (52 mg, 0.38 mmol) was added and stirred at 80 °C for 2 h then an additional $K_2CO_3$ (52 mg, 0.38 mmol) was added and stirred at 80 °C for 12 h. Purified by flash chromatography (40 g silica gel, eluting 15-100% EtOAc in petroleum ether) and to provide the title compound (0.15 g). LCMS (Method 3): 1.84 min, 597.3 $[M+H]^+$.

**Intermediate 119:** Methyl 2-((10*S*,13*S*)-2$^6$-methyl-11-oxo-10-(2-oxo-5-(trifluoromethyl)-pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00277]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 118** (0.15 g, 0.23 mmol) in DCE (26 mL) and Grubbs II (19 mg, 0.03 mmol) at RT for 4 h. Purified by flash chromatography (25 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (90 mg). LCMS (Method 3): 1.73 min, 569.3 $[M+H]^+$.

**Intermediate 120:** Methyl 2-((10*S*,13*S*)-2$^6$-methyl-11-oxo-10-(2-oxo-5-(trifluoromethyl)-pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00278]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 119** (90 mg, 0.15 mmol) and 10% palladium on carbon (1.6 mg) in MeOH (12 mL) under a hydrogen atmosphere at RT for 5 h, to provide the title compound (82 mg). LCMS (Method 3): 1.78 min, 571.2 $[M+H]^+$.

**Intermediate 121:** (2-(Benzyloxy)-6-methylphenyl)boronic acid

**[00279]** A mixture of magnesium (0.53 g, 21.7 mmol) and iodine (0.11 g, 0.45 mmol) was heated at 30 °C under nitrogen. To this was added a few drops of 1-(benzyloxy)-2-bromo-3-methylbenzene (5.0 g, 18.0 mmol, CAS 1381944-69-9) in THF (10 mL) and the mixture heated to 47 °C then the remainder of the solution was added over 5 min. Additional THF (4 mL) was added and the mixture stirred at 47 °C for 2 h until the majority of magnesium was consumed. The mixture was cooled to RT. This solution was added dropwise to a solution of trimethyl borate (3.75 g, 4.02 mmol) in THF (20 mL) at -30 °C over 5 min. The mixture was stirred at -30 °C for 2 h. The mixture was adjusted to pH 4 with 2 M aqueous HCl and the mixture was stirred at RT for 30 min. The mixture was extracted with DCM then the organics were washed with water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was recrystallised from diethyl ether / petroleum ether, filtered and dried under vacuum to provide the title compound (0.88 g). LCMS (Method 7): 1.64 min, 243.0 $[M+H]^+$. Additional product (0.45 g) was isolated from the filtrate then purified by flash chromatography (80 g silica gel, eluting 20% EtOAc in petroleum ether).

**Intermediate 122:** (*R*,*E*)-*N*-(5-Bromo-2-fluoro-3-methylbenzylidene)-2-methylpropane-2-sulfinamide

**[00280]** Prepared in an analogous manner to **Intermediate 102** using 5-bromo-2-fluoro-3-methylbenzaldehyde (1.50 g, 6.91 mmol, CAS 903875-64-9), (*R*)-2-methylpropane-2-sulfinimide (0.92 g, 7.60 mmol, CAS 196929-78-9) and titanium ethoxide (2.36 g, 10.4 mmol) in THF (25 mL) at 40 °C for 2.5 h, to provide the title compound (90 mg). LCMS (Method 7): 2.29 min, 322.0 $[M+H]^+$.

**Intermediate 123:** Ethyl (*S*)-3-(5-bromo-2-fluoro-3-methylphenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

**[00281]** Prepared in an analogous manner to **Intermediate 104** using zinc (0.69 g, 10.6 mmol) chlorotrimethylsilane (0.15 mL, 1.22 mmol) and ethyl bromoacetate (1.69 mL, 15.2 mmol) in THF (25 mL) at 60 °C for 1 h, then **Intermediate 122** (1.95 g, 6.09 mmol) in THF (25 mL) at RT for 16 h. Purified by flash chromatography (80 g silica gel, eluting 1-10% MeOH in DCM) to provide the title compound (1.55 g). LCMS (Method 8): 2.07 min, 410.3 $[M+H]^+$.

**Intermediate 124:** Ethyl (*S*)-3-(2'-(benzyloxy)-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

**[00282]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 121** (0.80 g, 3.14 mmol), **Intermediate 123** (1.39 g, 3.14 mmol), $K_2CO_3$ (1.08 g, 7.85 mmol) and $Pd(dppf)Cl_2$ (0.11 g, 0.15 mmol) in 1,4-dioxane (30 mL), and water (3 mL) at 85 °C for 2.5 h. Purified by flash chromatography (40 g silica gel, eluting 50% EtOAc in petroleum ether) to provide the title compound (1.41 g). LCMS (Method 7): 2.49 min, 526.2 $[M+H]^+$.

**Intermediate 125:** Ethyl (*S*)-3-amino-3-(2'-(benzyloxy)-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00283]** A suspension of **Intermediate 124** (1.13 g, 2.15 mmol) in ethanol (10 mL) and 4 M HCl in 1,4-dioxane (10.75 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.98 g). LCMS (Method 8): 1.70 min, 422.4 $[M+H]^+$.

**Intermediate 126:** Ethyl (*S*)-3-(2'-(benzyloxy)-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00284]** To a stirred suspension of **Intermediate 125** (0.98 g, 1.17 mmol) and Boc anhydride (0.46 g, 2.09 mmol) in DCM (25 mL) was added DIPEA (0.3 mL, 3.48 mmol) and the mixture stirred for 16 h at RT. The reaction mixture was diluted with DCM and washed with 1 M aqueous HCl, water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (40 g silica gel, eluting 20-

40% EtOAc in petroleum ether) to provide the title compound (0.75 g). LCMS (Method 8): 2.56 min, 520.5 $[M-H]^-$.

**Intermediate 127:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2'-hydroxy-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00285]** To a stirred solution of **Intermediate 126** (0.68 g, 1.29 mmol) in ethanol (25 mL) was added ammonium formate (1.63 g, 25.9 mmol) and 10% palladium on carbon (0.28 g, 0.26 mmol) and the mixture was stirred for 2 h at reflux. Additional ammonium formate (1.63 g, 25.9 mmol) was added and heating continued for 1.5 h. Additional 10% palladium on carbon (0.28 g, 0.26 mmol) was added and heating continued for 2 h. The mixture was cooled to RT, diluted with EtOAc and water and filtered through Celite®. The organic layer was separated and the aqueous extracted with EtOAc. The combined organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (0.52 g). LCMS (Method 8): 2.19 min, 430.5 $[M-H]^-$.

**Intermediate 128:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00286]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 127** (0.56 g, 1.12 mmol), $K_2CO_3$ (0.19 g, 1.35 mmol) and 5-bromopent-1-ene (0.13 mL, 1.12 mmol) in MeCN (15 mL) at reflux for 8 h. Extra $K_2CO_3$ (0.19 g, 1.35 mmol) and 5-bromopent-1-ene (0.13 mL, 1.12 mmol) was added and heating continued for 4 h. Extra $K_2CO_3$ (0.16 g, 1.12 mmol) was added and heating continued for 5 h, to provide the title compound (0.53 g). LCMS (Method 8): 2.63 min, 522.5 $[M+Na]^+$.

**Intermediate 129:** Ethyl (*S*)-3-amino-3-(4-fluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00287]** To a suspension of **Intermediate 128** (0.53 g, 0.98 mmol) in 1,4-dioxane (5 mL) was added 4 M HCl in 1,4-dioxane (4.9 mL) and this was stirred at RT for 3 h. The mixture was concentrated under reduced pressure to provide the title compound (0.43 g). LCMS (Method 8): 1.71 min, 400.4 $[M+H]^+$.

**Intermediate 130:** Ethyl (*S*)-3-(4-fluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00288]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 129** (0.43 g, 0.98 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.13 g, 0.98 mmol, CAS 413622-10-3), DIPEA (0.51 mL, 2.93 mmol), HOBt (0.13 g, 0.98 mmol) and EDCI (0.21 g, 1.08 mmol) in MeCN (20 mL) at RT for 4 h followed by additional (2*R*)-2-hydroxypent-4-enoic acid (0.13 g, 0.98 mmol, CAS 413622-10-3) and EDCI (0.19 g, 0.98 mmol) and stirring at RT for 3 h. Purified

by flash chromatography (24 g silica gel, eluting 25-50% EtOAc in petroleum ether) to provide the title compound (0.27 g). LCMS (Method 6): 1.83 min, 498.5 $[M+H]^+$.

**Intermediate 131:** Ethyl (*S*)-3-(4-fluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00289]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 130** (0.27 g, 0.54 mmol), triethylamine (0.15 mL, 1.08 mmol) and methanesulfonyl chloride (0.06 mL, 0.81 mmol) in DCM (5.4 mL) at RT for 0.5 h, to provide the title compound (0.31 g). LCMS (Method 3): 1.84 min, 576.3 $[M+H]^+$.

**Intermediate 132:** Ethyl (*S*)-3-(4-fluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00290]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 131** (0.31 g, 0.54 mmol), pyridin-2-ol (0.11 g, 1.18 mmol, CAS 142-08-5) and $K_2CO_3$ (0.17 g, 1.19 mmol) in MeCN (5.4 mL) at 85 °C for 1 h. Additional $K_2CO_3$ (0.17 g, 1.19 mmol) was added and stirred at 95 °C for 9 h. Purified by flash chromatography (12 g silica gel, eluting 0-100% EtOAc in petroleum ether) and to provide the title compound (0.14 g). LCMS (Method 3): 1.82 min, 575.3 $[M+H]^+$.

**Intermediate 133:** Ethyl 2-((10*S*,13*S*)-$1^4$-fluoro-$1^5$,$2^6$-dimethyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00291]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 132** (0.14 g, 0.24 mmol) in DCE (0.11 L) and Grubbs II (20.7 mg, 0.02 mmol) at 40 °C for 4 h. Purified by flash chromatography (24 g silica gel, eluting 50-80% EtOAc in petroleum ether) to provide the title compound (0.10 g). LCMS (Method 8): 2.22 min, 547.5 $[M+H]^+$.

**Intermediate 134:** Ethyl 2-((10*S*,13*S*)-$1^4$-fluoro-$1^5$,$2^6$-dimethyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00292]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 133** (0.10 g, 0.18 mmol) and 10% palladium on carbon (19.5 mg) in MeOH (4 mL) under a hydrogen atmosphere at RT for 0.5 h, to provide the title compound (97 mg). LCMS (Method 9): 4.65 min, 549.6 $[M+H]^+$.

**Intermediate 135:** 5-(2-Methoxyvinyl)pyridin-2(1*H*)-one

**[00293]** To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (10.4 g, 30.5 mmol, CAS 4009-98-7) in 1,4-dioxane (49.5 mL) was added potassium *tert*-butoxide (1 M in THF, 50.8 mL, 50.8 mmol) dropwise, and the mixture was stirred at RT for 15 min. 6-Oxo-1*H*-pyridine-3-carbaldehyde (2.50 g, 20.3 mmol) was added as a solution in THF (16.5 mL) and

the mixture stirred for at RT for 16 h. The reaction mixture was diluted with water and the crude product extracted into EtOAc then 10% MeOH in DCM. The combined organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by reverse-phase chromatography (32 g C18, eluting 0-50% MeCN in water, 0.1% ammonia) to provide the title compound (0.93 g). LCMS (Method 4): 0.81 and 0.86 min, 152.0 $[M+H]^+$.

**Intermediate 136:** 5-(2,2-Dihydroxyethyl)pyridin-2(1*H*)-one

**[00294]** A suspension of **Intermediate 135** (0.30 g, 1.97 mmol) in formic acid (5.22 mL, 138 mmol) was stirred at 70 °C for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.27 g). $^1H$ NMR (400 MHz; $CD_3OD$) δ: 7.57 (dd, 1H), 7.28 (d, 1H), 6.49 (d, 1H), 4.59 (t, 1H), 2.71 – 2.59 (m, 2H).

**Intermediate 137:** 5-(2-(Dimethylamino)ethyl)pyridin-2(1*H*)-one

**[00295]** To a stirred solution of **Intermediate 136** (0.27 g, 1.97 mmol), dimethylamine (2 M solution in MeOH, 1.48 mL, 2.96 mmol) in MeOH (4.5 mL), DCM (1.0 mL) and AcOH (0.14 mL) was added 4 Å molecular sieves and the mixture was stirred at RT for 30 min. STAB (1.25 g, 5.91 mmol) was added and the mixture stirred at RT for 16 h. Additional dimethylamine (2 M solution in MeOH, 1.48 mL, 2.96 mmol) and STAB (1.25 g, 5.91 mmol) were added and stirred at RT for 6 h. The mixture was filtered and the filtrate concentrated under reduced pressure. The crude product was purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 1 M ammonia in MeOH) to provide the title compound (0.24 g). LCMS (Method 4): 0.86 min, 167.0 $[M+H]^+$.

**Intermediate 138:** Methyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00296]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 114** (0.25 g, 0.47 mmol), **Intermediate 137** (0.09 g, 0.57 mmol) and $K_2CO_3$ (0.13 g, 0.94 mmol) in MeCN (12 mL) at 90 °C for 10 h. Additional $K_2CO_3$ (0.13 g, 0.94 mmol) was added and stirred at 90 °C for 40 h. Purified by flash chromatography (24 g silica gel, eluting 5-10% MeOH in DCM with 0.5% ammonia in MeOH) to provide the title compound (0.09 g). LCMS (Method 5): 2.10 min, 600.1 $[M+H]^+$.

**Intermediate 139:** Methyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00297]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 138** (89 mg, 0.15 mmol) in DCE (64 mL) and Grubbs II (12.6 mg, 14.8 µmol) at 40 °C for 4 h. Additional Grubbs II (12.6 mg, 14.8 µmol) was added and stirred at 40 °C for 2 h. Purified by flash

chromatography (12 g silica gel, eluting 5-10% MeOH in DCM with 0.1% ammonia in MeOH) to provide the title compound (66 mg). LCMS (Method 5): 2.07 min, 570.5 $[M-H]^-$.

**Intermediate 140:** Methyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00298]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 139** (48 mg, 0.08 mmol) and 10% palladium on carbon (9 mg) in MeOH (8 mL) under a hydrogen atmosphere at RT for 15 min. Additional 10% palladium on carbon (9 mg) added and stirred under hydrogen at RT for 20 min, to provide the title compound (67 mg). LCMS (Method 10): 4.33 min, 572.5 $[M-H]^-$.

**Intermediate 141:** Methyl (*S*)-3-(2'-(allyloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00299]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 76** (0.43 g, 0.86 mmol), **Intermediate 137** (0.17 g, 1.03 mmol) and $K_2CO_3$ (0.24 g, 1.72 mmol) in MeCN (5 mL) at 90 °C for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-20% MeOH in DCM) to provide the title compound (0.14 g). LCMS (Method 11): 2.10 min, 572.1 $[M+H]^+$.

**Intermediate 142:** Methyl 2-((8*S*,11*S*)-8-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphan-5-en-11-yl)acetate

**[00300]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 141** (0.14 g, 0.24 mmol) in DCE (50 mL) and Grubbs II (20 mg, 24.5 µmol) at 40 °C for 96 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.14 g). LCMS (Method 5): 2.07 min, 544.3 $[M+H]^+$.

**Intermediate 143:** Methyl 2-((8*S*,11*S*)-8-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetate

**[00301]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 142** (0.14 g, 0.18 mmol) and 10% palladium on carbon (19 mg) in MeOH (5 mL) under a hydrogen atmosphere at RT for 5 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM). This material was then treated with 10% palladium on carbon (12 mg) in MeOH (4 mL) under a hydrogen atmosphere at RT for 15 min, to provide the title compound (12 mg). LCMS (Method 5): 1.95 min, 546.3 $[M+H]^+$.

**Intermediate 144:** Methyl (*S*)-3-(4'-bromo-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00302]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 2** (0.40 g, 0.99 mmol), 5-bromo-2-iodo-3-methylphenol (0.31 g, 0.99 mmol, CAS 2091225-92-0), $Na_2CO_3$ (0.26 g, 2.48 mmol) and $Pd(dppf)Cl_2$ (81 mg, 0.10 mmol) in 1,4-dioxane (9.3 mL), and

water (3.1 mL) at 55 °C for 2.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-35% EtOAc in petroleum ether) to provide the title compound (0.38 g). LCMS (Method 6): 1.66 min, 486.2 $[M+Na]^+$.

**Intermediate 145:** Methyl (*S*)-3-(4'-bromo-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00303]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 144** (0.32 g, 0.69 mmol), $K_2CO_3$ (0.12 g, 0.90 mmol) and 5-bromopent-1-ene (0.10 mL, 0.83 mmol) in MeCN (36 mL) at reflux for 18 h, to provide the title compound (0.34 g). LCMS (Method 6): 2.03 min, 556.2 $[M+Na]^+$.

**Intermediate 146:** Methyl (*S*)-3-amino-3-(4'-bromo-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00304]** A suspension of **Intermediate 145** (0.29 g, 0.54 mmol) in 4 M HCl in 1,4-dioxane (4.1 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure to provide the title compound (0.43 g). LCMS (Method 12): 1.86 min, 456.1 $[M+Na]^+$.

**Intermediate 147:** Methyl (*S*)-3-(4'-bromo-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00305]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 146** (0.66 g, 1.40 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.16 g, 1.40 mmol, CAS 413622-10-3), DIPEA (0.73 mL, 4.20 mmol), HOBt (0.21 g, 1.40 mmol) and EDCI (0.32 g, 1.68 mmol) in DMF (12 mL) at RT for 18 h. Purified by flash chromatography (12 g silica gel, eluting 15-55% EtOAc in petroleum ether) to provide the title compound (0.33 g). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, 1H), 7.29 (t, 1H), 7.18 (d, 1H), 7.05 – 6.98 (m, 2H), 6.97 (d, 1H), 6.85 (d, 1H), 5.76 – 5.51 (m, 2H), 5.40 (dt, 1H), 5.14 – 5.02 (m, 2H), 4.75 – 4.60 (m, 2H), 4.11 (dt, 1H), 3.76 (t, 2H), 3.53 (s, 3H), 2.88 (dd, 1H), 2.78 (dd, 1H), 2.63 – 2.52 (m, 2H), 2.34 (dt, 1H), 1.94 (s, 3H), 1.87 (q, 2H), 1.66 – 1.48 (m, 2H).

**Intermediate 148:** Methyl (*S*)-3-(4'-bromo-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00306]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 147** (0.39 g, 0.74 mmol), triethylamine (0.21 mL, 1.47 mmol) and methanesulfonyl chloride (0.09 mL, 1.10 mmol) in DCM (6 mL) at RT for 18 h. Purified by flash chromatography (12 g silica gel, eluting 15-55% EtOAc in petroleum ether) to provide the title compound (0.45 g). LCMS (Method 4): 1.99 min, 606.1 $[M-H]^-$.

**Intermediate 149:** Methyl (*S*)-3-(4'-bromo-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00307]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 148** (0.45 g, 0.67 mmol), pyridin-2-ol (0.14 g, 1.48 mmol) and $K_2CO_3$ (0.28 g, 2.02 mmol) in MeCN (10 mL) at 90 °C for 16 h. Purified by flash chromatography (12 g silica gel, eluting 10-100% EtOAc in petroleum ether) to provide the title compound (0.15 g). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, 1H), 7.47 (dd, 1H), 7.33 – 7.14 (m, 3H), 7.09 – 6.99 (m, 2H), 6.96 (d, 1H), 6.84 (d, 1H), 6.45 (d, 1H), 6.18 (td, 1H), 5.67 – 5.45 (m, 3H), 5.32 (q, 1H), 4.97 (dd, 1H), 4.92 – 4.77 (m, 3H), 3.76 (t, 2H), 3.41 (s, 3H), 2.75 – 2.62 (m, 3H), 2.52 (dt, 1H), 1.94 (s, 3H), 1.87 (q, 2H), 1.59 – 1.56 (m, 2H).

**Intermediate 150:** Methyl 2-((10*S*,13*S*)-2$^4$-bromo-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00308]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 149** (0.17 g, 0.28 mmol) in DCE (30 mL) and Grubbs II (24 mg, 28.4 µmol) at 40 °C for 4 h. Purified by flash chromatography (25 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (90 mg). LCMS (Method 4): 1.84 min, 581.0 $[M+H]^+$.

**Intermediate 151:** Methyl 2-((10*S*,13*S*)-2$^4$-(3,6-dihydro-2*H*-pyran-4-yl)-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00309]** A mixture of **Intermediate 150** (85 mg, 0.15 mmol), 2-(3,6-dihydro-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (34 mg, 0.16 mmol, CAS 287944-16-5) and $Na_2CO_3$ (39 mg, 0.37 mmol) in 1,4-dioxane (4 mL) and water (2 mL) was degassed with nitrogen. To this was added Pd(dppf)$Cl_2$ (5.4 mg, 0.05 mmol) and the reaction mixture stirred at 80 °C for 16 h. The mixture was concentrated under reduced pressure then diluted with water and extracted into DCM. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (0.13 g). LCMS (Method 4): 1.68 min, 583.2 $[M+H]^+$.

**Intermediate 152:** 2-((10*S*,13*S*)-2$^4$-(3,6-Dihydro-2*H*-pyran-4-yl)-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetic acid

**[00310] Intermediate 151** (0.13 g, 0.15 mmol) was dissolved in MeOH (6 mL), THF (10 mL) and water (6 mL) then lithium hydroxide (7.9 mg, 0.33 mmol) was added and the solution stirred at RT for 2 h. Additional lithium hydroxide (7.9 mg, 0.33 mmol) was added and stirring continued at RT for 3 h. The mixture was concentrated under reduced pressure and the residue acidified with 2 M aqueous HCl and extracted with DCM. The organic layer was washed with brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (70 mg). LCMS (Method 4): 1.12 min, 569.1 $[M+H]^+$.

**Intermediate 153:** Methyl 2-((10*S*,13*S*)-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-2$^4$-(tetrahydro-2*H*-pyran-4-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00311]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 152** (70 mg, 0.12 mmol) and 10% palladium on carbon (13 mg) in MeOH (5 mL) under a hydrogen atmosphere at RT for 24 h, to provide the title compound (63 mg). LCMS (Method 12): 1.60 min, 587.4 $[M+H]^+$.

**Intermediate 154:** Benzyl (*S*)-3'-(1-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-6-methyl-[1,1'-biphenyl]-2-carboxylate

**[00312]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 2** (0.38 g, 0.94 mmol), benzyl 2-bromo-3-methylbenzoate (0.26 g, 0.86 mmol, CAS 291289-66-2), $Na_2CO_3$ (0.18 g, 1.71 mmol) and $Pd(dppf)Cl_2$ (63 mg, 0.09 mmol) in 1,4-dioxane (3 mL), and water (1.8 mL) at 85 °C for 16 h. Purified by flash chromatography (24 g silica gel, eluting 5-35% EtOAc in petroleum ether) to provide the title compound (0.25 g). LCMS (Method 4): 1.91 min, 404.1 $[M-Boc+H]^+$.

**Intermediate 155:** (*S*)-3'-(1-((*tert*-Butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-6-methyl-[1,1'-biphenyl]-2-carboxylic acid

**[00313]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 154** (0.25 g, 0.49 mmol) and 10% palladium on carbon (52 mg) in THF (15 mL) under a hydrogen atmosphere at RT for 16 h, to provide the title compound (0.19 g). LCMS (Method 3): 1.56 min, 314.0 $[M-Boc+H]^+$.

**Intermediate 156:** Methyl (*S*)-3-(2'-(allylcarbamoyl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00314]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 155** (96 mg, 0.23 mmol), allylamine (17.5 µL, 0.23 mmol), DIPEA (81 µL, 0.47 mmol), HOBt (36 mg, 0.23 mmol) and EDCI (54 mg, 0.28 mmol) in DMF (2 mL) at RT for 16 h, to provide the title compound (0.33 g). LCMS (Method 3): 1.59 min, 353.1 $[M-Boc+H]^+$.

**Intermediate 157:** Methyl (*S*)-3-(2'-(allylcarbamoyl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-aminopropanoate hydrochloride

**[00315]** A suspension of **Intermediate 156** (83 mg, 0.18 mmol) in 4 M HCl in 1,4-dioxane (2 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (71 mg). LCMS (Method 3): 1.07 min, 353.1 $[M+H]^+$.

**Intermediate 158:** Methyl (*S*)-3-(2'-(allylcarbamoyl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enamido)propanoate

**[00316]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 157** (71 mg, 0.18 mmol), *N*-Boc-*L*-allylglycine (39 mg, 0.18 mmol, CAS 90600-20-7), DIPEA (64 µL, 0.37 mmol), HOBt (28 mg, 0.18 mmol) and EDCI (42 mg, 0.22 mmol) in DMF (2 mL) at RT for 18 h, to provide the title compound (77 mg). LCMS (Method 3): 1.58 min, 550.2 $[M+H]^+$.

**Intermediate 159:** Methyl 2-((3*S*,6*S*)-6-((*tert*-butoxycarbonyl)amino)-1$^6$-methyl-5,12-dioxo-4,11-diaza-1(1,2),2(1,3)-dibenzenacyclododecaphan-8-en-3-yl)acetate

**[00317]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 158** (77 mg, 0.14 mmol) in DCE (5 mL) and Grubbs II (12 mg, 14 µmol) at 40 °C for 4 h. Purified by flash chromatography (12 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (51 mg). LCMS (Method 3): 1.42 min, 522.1 $[M+H]^+$.

**Intermediate 160:** Methyl 2-((3*S*,6*S*)-6-((*tert*-butoxycarbonyl)amino)-1$^6$-methyl-5,12-dioxo-4,11-diaza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetate

**[00318]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 159** (55 mg, 0.11 mmol) and 10% palladium on carbon (11 mg) in MeOH (10 mL) under a hydrogen atmosphere at RT for 3 h, to provide the title compound (47 mg). LCMS (Method 3): 1.40 min, 524.2 $[M+H]^+$.

**Intermediate 161:** Methyl 2-((3*S*,6*S*)-6-amino-1$^6$-methyl-5,12-dioxo-4,11-diaza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetate hydrochloride

**[00319]** A suspension of **Intermediate 160** (47 mg, 0.09 mmol) in 4 M HCl in 1,4-dioxane (2 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (41 mg). LCMS (Method 3): 1.05 min, 424.2 $[M+H]^+$.

**Intermediate 162:** Methyl 2-((3*S*,6*S*)-6-acetamido-1$^6$-methyl-5,12-dioxo-4,11-diaza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetate

**[00320]** Prepared in an analogous manner to **Intermediate 10** using **Intermediate 161** (41 mg, 0.09 mmol), triethylamine (27 µL, 0.20 mmol), acetyl chloride (7 µL, 0.10 mmol) in DCM (2 mL) at RT for 1 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (20 mg). LCMS (Method 3): 1.15 min, 466.2 $[M+H]^+$.

**Intermediate 163:** Methyl (*S*)-3-(2'-(but-3-en-1-ylcarbamoyl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00321]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 155** (97 mg, 0.23 mmol), but-3-en-1-amine (21 µL, 0.23 mmol), DIPEA (81 µL, 0.47 mmol), HOBt (36 mg, 0.23 mmol) and EDCI (54 mg, 0.28 mmol) in DMF (2 mL) at RT for 16 h. Purified by flash chromatography (12 g silica gel, eluting 50–100% EtOAc in petroleum ether) to provide the title compound (83 mg). LCMS (Method 3): 1.63 min, 367.1 $[M-Boc+H]^+$.

**Intermediate 164:** Methyl (*S*)-3-amino-3-(2'-(but-3-en-1-ylcarbamoyl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00322]** A suspension of **Intermediate 163** (83 mg, 0.18 mmol) in 4 M HCl in 1,4-dioxane (2 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (72 mg). LCMS (Method 3): 1.11 min, 367.1 $[M+H]^+$.

**Intermediate 165:** Methyl (*S*)-3-(2'-(but-3-en-1-ylcarbamoyl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enamido)propanoate

**[00323]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 164** (72 mg, 0.18 mmol), *N*-Boc-*L*-allylglycine (39 mg, 0.18 mmol, CAS 90600-20-7), DIPEA (62 µL, 0.36 mmol), HOBt (27 mg, 0.18 mmol) and EDCI (41 mg, 0.21 mmol) in DMF (2 mL) at RT for 4 h, to provide the title compound (67 mg). LCMS (Method 3): 1.57 min, 564.2 $[M+H]^+$.

**Intermediate 166:** Methyl 2-((3*S*,6*S*)-6-((*tert*-butoxycarbonyl)amino)-$1^6$-methyl-5,13-dioxo-4,12-diaza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00324]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 165** (67 mg, 0.12 mmol) in DCE (4 mL) and Grubbs II (10 mg, 12 µmol) at 40 °C for 4 h. Additional Grubbs II (10 mg, 12 µmol) was added in DCE (2 mL) at 40 °C for 3 h. Purified by flash chromatography (12 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (44 mg). LCMS (Method 4): 1.47 min, 536.2 $[M+H]^+$.

**Intermediate 167:** Methyl 2-((3*S*,6*S*)-6-((*tert*-butoxycarbonyl)amino)-$1^6$-methyl-5,13-dioxo-4,12-diaza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00325]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 166** (44 mg, 0.08 mmol) and 10% palladium on carbon (8.7 mg) in MeOH (10 mL) under a hydrogen atmosphere at RT for 2 h, to provide the title compound (36 mg). LCMS (Method 4): 1.53 min, 538.2 $[M+H]^+$

**Intermediate 168:** Methyl 2-((3*S*,6*S*)-6-amino-$1^6$-methyl-5,13-dioxo-4,12-diaza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate hydrochloride

**[00326]** A suspension of **Intermediate 167** (36 mg, 0.07 mmol) in 4 M HCl in 1,4-dioxane (2 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (32 mg). LCMS (Method 4): 1.17 min, 438.2 $[M+H]^+$.

**Intermediate 169:** Methyl 2-((3*S*,6*S*)-6-acetamido-$1^6$-methyl-5,13-dioxo-4,12-diaza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00327]** Prepared in an analogous manner to **Intermediate 10** using **Intermediate 168** (32 mg, 0.07 mmol), triethylamine (21 µL, 0.15 mmol), acetyl chloride (5 µL, 0.07 mmol) in DCM

(5 mL) at RT for 0.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (39 mg). LCMS (Method 4): 1.11 min, 480.2 $[M+H]^+$.

**Intermediate 170:** Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-(hex-5-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00328]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 3** (0.20 g, 0.52 mmol), $K_2CO_3$ (0.18 g, 1.30 mmol) and 6-bromohex-1-ene (0.14 mL, 1.04 mmol) in MeCN (5 mL) at reflux for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.14 g). LCMS (Method 4): 2.05 min, 368.2 $[M\text{-}Boc+H]^+$.

**Intermediate 171:** Methyl (*S*)-3-amino-3-(2'-(hex-5-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00329]** A suspension of **Intermediate 170** (0.14 g, 0.31 mmol) in 4 M HCl in 1,4-dioxane (3 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.13 g). LCMS (Method 4): 1.85 min, 368.2 $[M+H]^+$.

**Intermediate 172:** Methyl (*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enamido)-3-(2'-(hex-5-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00330]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 171** (0.13 g, 0.33 mmol), *N*-Boc-*L*-allylglycine (71 mg, 0.33 mmol, CAS 90600-20-7), DIPEA (0.17 mL, 1.00 mmol), HOBt (51 mg, 0.33 mmol) and EDCI (76 mg, 0.40 mmol) in DMF (2 mL) at RT for 4 h, to provide the title compound (0.18 g). LCMS (Method 4): 2.02 min, 565.3 $[M+H]^+$.

**Intermediate 173:** Methyl 2-((11*S*,14*S*,*E*)-11-((*tert*-butoxycarbonyl)amino)-$2^6$-methyl-12-oxo-3-oxa-13-aza-1(1,3),2(1,2)-dibenzenacyclotetradecaphan-8-en-14-yl)acetate

**[00331]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 172** (0.17 g, 0.30 mmol) in DCE (0.15 L) and Grubbs II (30 mg, 0.12 mmol) at 40 °C for 2.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.11 g). LCMS (Method 4): 1.91 min, 537.1 $[M+H]^+$.

**Intermediate 174:** Methyl 2-((11*S*,14*S*,*E*)-11-amino-$2^6$-methyl-12-oxo-3-oxa-13-aza-1(1,3),2(1,2)-dibenzenacyclotetradecaphan-8-en-14-yl)acetate hydrochloride

**[00332]** A suspension of **Intermediate 173** (30 mg, 0.06 mmol) in 4 M HCl in 1,4-dioxane (3 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (26 mg). LCMS (Method 4): 1.62 min, 437.1 $[M+H]^+$.

**Intermediate 175:** Methyl 2-((11*S*,14*S*,*E*)-11-acetamido-$2^6$-methyl-12-oxo-3-oxa-13-aza-1(1,3),2(1,2)-dibenzenacyclotetradecaphan-8-en-14-yl)acetate

**[00333]** Prepared in an analogous manner to **Intermediate 10** using **Intermediate 174** (28 mg, 0.06 mmol), triethylamine (18 µL, 0.13 mmol), acetyl chloride (5 µL, 0.07 mmol) in DCM (3 mL) at RT for 1 h, to provide the title compound (28 mg). LCMS (Method 4): 1.65 min, 479.3 $[M+H]^+$.

**Intermediate 176:** Methyl 2-((11*S*,14*S*)-11-((*tert*-butoxycarbonyl)amino)-2$^6$-methyl-12-oxo-3-oxa-13-aza-1(1,3),2(1,2)-dibenzenacyclotetradecaphane-14-yl)acetate

**[00334]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 173** (80 mg, 0.15 mmol) and 10% palladium on carbon (16 mg) in MeOH (19 mL) under a hydrogen atmosphere at RT for 3 h, to provide the title compound (77 mg). LCMS (Method 12): 1.82 min, 539.4 $[M+H]^+$.

**Intermediate 177:** Methyl 2-((11*S*,14*S*)-11-amino-2$^6$-methyl-12-oxo-3-oxa-13-aza-1(1,3),2(1,2)-dibenzenacyclotetradecaphane-14-yl)acetate hydrochloride

**[00335]** A suspension of **Intermediate 176** (77 mg, 0.14 mmol) in 4 M HCl in 1,4-dioxane (7.7 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (77 mg). LCMS (Method 4): 1.66 min, 439.2 $[M+H]^+$.

**Intermediate 178:** Methyl 2-((11*S*,14*S*)-11-acetamido-2$^6$-methyl-12-oxo-3-oxa-13-aza-1(1,3),2(1,2)-dibenzenacyclotetradecaphane-14-yl)acetate

**[00336]** Prepared in an analogous manner to **Intermediate 10** using **Intermediate 177** (68 mg, 0.14 mmol), triethylamine (44 µL, 0.32 mmol), acetyl chloride (11 µL, 0.16 mmol) in DCM (5 mL) at RT for 1 h, to provide the title compound (69 mg). LCMS (Method 4): 1.69 min, 481.2 $[M+H]^+$.

**Intermediate 179:** Methyl 3-((*tert*-butoxycarbonyl)amino)-3-(5-(4-fluoro-2-hydroxy-6-methylphenyl)pyridin-3-yl)propanoate

**[00337]** Prepared in an analogous manner to **Intermediate 92** using **Intermediate 91** (0.50 g, 1.39 mmol), bis(pinacolato)diboron (0.53 g, 2.09 mmol), potassium acetate (0.34 g, 3.48 mmol), and Pd(dppf)$Cl_2$ (51 mg, 0.07 mmol) in 1,4-dioxane (6.5 mL) at 100 °C for 1 h, then $Na_2CO_3$ (0.30 g, 2.78 mmol) in water (6.6 mL) and 2-bromo-5-fluoro-3-methylphenol (0.34 g, 1.67 mmol, CAS 1807192-21-7) were added followed by heating at 100 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 40-100% EtOAc in petroleum ether) to provide the title compound (0.34 g). LCMS (Method 12): 1.26 min, 405.4 $[M+H]^+$.

**Intermediate 180:** Methyl 3-((*tert*-butoxycarbonyl)amino)-3-(5-(4-fluoro-2-methyl-6-(pent-4-en-1-yloxy)phenyl)pyridin-3-yl)propanoate

**[00338]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 179** (0.34 g, 0.84 mmol), $K_2CO_3$ (0.29 g, 2.10 mmol) and 5-bromopent-1-ene (0.11 mL, 0.92 mmol) in MeCN (7 mL) at reflux for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0 - 50% EtOAc in petroleum ether) to provide the title compound (0.14 g). LCMS (Method 4): 1.83 min, 473.3 $[M+H]^+$.

**Intermediate 181:** Methyl 3-amino-3-(5-(4-fluoro-2-methyl-6-(pent-4-en-1-yloxy)phenyl)pyridin-3-yl)propanoate hydrochloride

**[00339]** A suspension of **Intermediate 180** (0.18 g, 0.38 mmol) in 4 M HCl in 1,4-dioxane (1.7 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.16 g). LCMS (Method 4): 1.57 min, 373.2 $[M+H]^+$.

**Intermediate 182:** Methyl 3-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)pent-4-enamido)-3-(5-(4-fluoro-2-methyl-6-(pent-4-en-1-yloxy)phenyl)pyridin-3-yl)propanoate

**[00340]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 181** (0.16 g, 0.40 mmol), *N*-methyl-*N*-Boc-*L*-allylglycine (96 mg, 0.42 mmol, CAS 136092-76-7), DIPEA (0.20 mL, 1.14 mmol), HOBt (58 mg, 0.38 mmol) and EDCI (87 mg, 0.46 mmol) in DMF (3 mL) at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-70% EtOAc in petroleum ether) to provide the title compound (0.14 g). LCMS (Method 4): 1.88 min, 584.3 $[M+H]^+$.

**Intermediate 183:** Methyl 2-((10*S*)-10-((*tert*-butoxycarbonyl)(methyl)amino)-$2^4$-fluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphan-7-en-13-yl)acetate

**[00341]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 182** (0.14 g, 0.25 mmol) in DCE (141 mL) and Grubbs II (25 mg, 0.03 mmol) at 40 °C for 48 h. Purified by flash chromatography (12 g silica gel, eluting 0-7% MeOH in DCM) to provide the title compound (64 mg). LCMS (Method 4): 1.78 min, 556.3 $[M+H]^+$.

**Intermediate 184:** Methyl 2-((10*S*)-10-((*tert*-butoxycarbonyl)(methyl)amino)-$2^4$-fluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetate

**[00342]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 183** (64 mg, 0.12 mmol) and 10% palladium on carbon (12 mg) in MeOH (12 mL) under a hydrogen atmosphere at RT for 1 h, to provide the title compound (54 mg). LCMS (Method 4): 1.83 and 1.85 min, 558.3 $[M+H]^+$.

**Intermediate 185:** Methyl 2-((10*S*)-$2^4$-fluoro-$2^6$-methyl-10-(methylamino)-11-oxo-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetate hydrochloride

**[00343]** A suspension of **Intermediate 184** (54 mg, 0.10 mmol) in 4 M HCl in 1,4-dioxane (2 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.16 g). LCMS (Method 4): 1.48 and 1.56 min, 458.3 $[M+H]^+$.

**Intermediate 186:** Methyl 2-((10*S*)-2$^4$-fluoro-2$^6$-methyl-10-(*N*-methylacetamido)-11-oxo-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetate

**[00344]** Prepared in an analogous manner to **Intermediate 10** using **Intermediate 185** (49 mg, 0.10 mmol), triethylamine (30 µL, 0.22 mmol), acetyl chloride (8 µL, 0.11 mmol) in DCM (1 mL) at RT for 2 h, to provide the title compound (49 mg). LCMS (Method 7): 1.77 min, 500.3 $[M+H]^+$.

**Intermediate 187:** Methyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(4'-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00345]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 84** (0.10 g, 0.18 mmol), **Intermediate 137** (39 mg, 0.24 mmol) and $K_2CO_3$ (76 mg, 0.55 mmol) in MeCN (5 mL) at 90 °C for 2 h. Additional $K_2CO_3$ (76 mg, 0.55 mmol) was added and stirred at 90 °C for 16 h. Purified by flash chromatography (4 g silica gel, eluting 5-10% MeOH in DCM with 0.5% ammonia in MeOH) to provide the title compound (50 mg). LCMS (Method 14): 5.01 min, 618.3 $[M+H]^+$.

**Intermediate 188:** Methyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00346]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 187** (50 mg, 0.06 mmol) in DCE (30 mL) and Grubbs II (5.3 mg, 6.2 µmol) at 40 °C for 4 h. Additional Grubbs II (2.6 mg, 3.1 µmol) was added and heating continued at 40 °C for 45 min. Purified by flash chromatography (4 g silica gel, eluting 5-10% MeOH in DCM with 0.5% ammonia) to provide the title compound (20 mg). LCMS (Method 15): 2.29 min, 590.2 $[M+H]^+$.

**Intermediate 189:** Methyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00347]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 188** (17 mg, 0.03 mmol) and 10% palladium on carbon (3 mg) in MeOH (2.4 mL) under a hydrogen atmosphere at RT for 15 min, to provide the title compound (15 mg). LCMS (Method 15): 2.36 min, 592.2 $[M+H]^+$.

**Intermediate 190:** 5-(2-(Pyrrolidin-1-yl)ethyl)pyridin-2(1*H*)-one

**[00348]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 136** (0.71 g, 4.59 mmol), pyrrolidine (1.13 mL, 13.8 mmol) in MeOH (7 mL), DCM (56 mL) and 4 Å molecular sieves at RT for 30 min, then STAB (2.92 g, 13.8 mmol) at RT for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-20 1 M ammonia MeOH in DCM) then by reverse phase chromatography (38 g C18, 0-50% MeCN in 0.1% aqueous ammonia) to provide the title compound (0.34 g). LCMS (Method 12): 0.82 min, 193.1 $[M+H]^+$.

**Intermediate 191:** Methyl (*S*)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00349]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 114** (0.18 g, 0.30 mmol), **Intermediate 190** (58 mg, 0.30 mmol) and $K_2CO_3$ (0.12 g, 0.91 mmol) in MeCN (1 mL) at 80 °C for 22 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (49 mg). LCMS (Method 8): 1.70 min, 624.7 $[M-H]^-$.

**Intermediate 192:** Methyl 2-((10*S*,13*S*)-2$^6$-methyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00350]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 191** (49 mg, 0.08 mmol) in DCE (39 mL) and Grubbs II (6.7 mg, 7.8 µmol) at 40 °C for 3 h. Additional Grubbs II (6.7 mg, 7.8 µmol) was added and heating continued at 40 °C for 6 h. Purified by flash chromatography (12 g silica gel, eluting 8% MeOH in DCM with 0.5% ammonia) to provide the title compound (23 mg). LCMS (Method 8): 1.56 min, 596.6 $[M-H]^-$.

**Intermediate 193:** Methyl 2-((10*S*,13*S*)-2$^6$-methyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00351]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 192** (47 mg, 0.06 mmol) and 10% palladium on carbon (6.4 mg) in MeOH (4 mL) under a hydrogen atmosphere at RT for 40 min. Additional 10% palladium on carbon (6.4 mg) was added and stirring continued under a hydrogen atmosphere at RT for 40 min, to provide the title compound (35 mg). LCMS (Method 11): 2.52 min, 598.6 $[M-H]^-$.

**Intermediate 194:** Methyl (*S*)-3-(2'-(but-3-en-1-yloxy)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(4-oxoquinazolin-3(4*H*)-yl)hex-5-enamido)propanoate

**[00352]** Prepared in an analogous manner to **Intermediate 57** using **Intermediate 56** (0.47 g, 0.89 mmol), quinazolin-4-ol (0.29 g, 1.95 mmol, CAS 491-36-1) and $K_2CO_3$ (0.37 g, 2.66 mmol) in MeCN (20 mL) at 95 °C for 1 h. Additional $K_2CO_3$ (0.37 g, 2.66 mmol) was added

and heating continued for 2 h. Purified by flash chromatography (24 g silica gel, eluting 0 - 100% EtOAc in petroleum ether) to provide the title compound (0.32 g). LCMS (Method 17): 2.40 min, 580.3 $[M+H]^+$.

**Intermediate 195:** Methyl 2-((10*S*,13*S*)-2$^6$-methyl-11-oxo-10-(4-oxoquinazolin-3(4*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-6-en-13-yl)acetate

**[00353]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 194** (0.35 g, 0.61 mmol) in DCE (31 mL) and Grubbs II (51 mg, 0.06 mmol) at 40 °C for 1 h. Quenched with ethyl vinyl ether (0.06 mL, 0.61 mmol). Purified by flash chromatography (25 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (0.17 g). LCMS (Method 3): 1.75 min, 552.2 $[M+H]^+$.

**Intermediate 196:** Methyl 2-((10*S*,13*S*)-2$^6$-methyl-11-oxo-10-(4-oxoquinazolin-3(4*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00354]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 195** (0.17 g, 0.31 mmol) and 10% palladium on carbon (32 mg) in MeOH (5 mL) under a hydrogen atmosphere at RT for 2 h to provide the title compound (0.12 g). LCMS (Method 15): 2.24 min, 554.2 $[M+H]^+$.

**Intermediate 197:** (*E*)-5-(2-Ethoxyvinyl)-3-fluoro-2-methoxypyridine

**[00355]** A solution of 5-bromo-3-fluoro-2-methoxypyridine (1.07 g, 5.18 mmol, CAS 124432-70-8) and 2-[(*E*)-2-ethoxyvinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.54 g, 7.70 mmol, CAS 1201905-61-4) in 1,4-dioxane (18 mL) and water (6 mL) was degassed with nitrogen. To the solution was then added $K_2CO_3$ (2.15 g, 15.5 mmol) followed by $Pd(PPh_3)_4$ (0.30 g, 0.26 mmol) and the reaction mixture stirred at 100 °C for 3 h. The mixture was cooled and filtered through Celite®, washing with EtOAc and water. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel 40 g, eluting 0-80% EtOAc in petroleum ether) to provide the title compound (0.94 g). LCMS (Method 4): 1.48 min, 198.0 $[M+H]^+$.

**Intermediate 198:** 2-(5-Fluoro-6-methoxypyridin-3-yl)acetaldehyde

**[00356]** A solution of **Intermediate 197** (0.15 g, 0.77 mmol) in DCE (3.1 mL) and TFA (0.59 mL) was stirred at 35 °C for 3 h. The mixture was cooled and concentrated under reduced pressure to provide the title compound (0.12 g). LCMS (Method 4): 1.04 min, 169.9 $[M+H]^+$.

**Intermediate 199:** 2-(5-Fluoro-6-methoxypyridin-3-yl)-N,N-dimethylethan-1-amine

**[00357]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 198** (0.25 g, 1.49 mmol), dimethylamine (2 M in THF, 0.89 mL, 1.78 mmol), triethylamine (0.41 mL, 2.97

mmol) in DCM (9.2 mL) and 4 Å molecular sieves at RT for 3 h, then STAB (0.63 g, 2.97 mmol) at RT for 18 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% 1 M ammonia MeOH in DCM) then by reverse phase chromatography (32 g C18, 5-60% MeCN in 0.1% aqueous ammonia) to provide the title compound (63 mg). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.76 (s, 1H), 7.22 (d, 1H), 3.99 (s, 3H), 2.71 (dd, 2H), 2.51 (dd, 2H), 2.29 (s, 6H).

**Intermediate 200:** 5-(2-(Dimethylamino)ethyl)-3-fluoropyridin-2(1*H*)-one

**[00358]** A solution of **Intermediate 199** (60 mg, 0.30 mmol) in 33% HBr in AcOH (1.05 mL, 6.06 mmol) was stirred at 85 °C for 2 h. The mixture was cooled and concentrated under reduced pressure. The crude product was purified by catch and release chromatography (1 g SCX, eluting MeOH followed by 1 M ammonia in MeOH) to provide the title compound (40 mg). $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.29 (dd, 1H), 7.03 (d, 1H), 2.53 – 2.48 (m, 2H), 2.46 – 2.42 (m, 2H), 2.20 (s, 6H).

**Intermediate 201:** Methyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00359]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 114** (0.17 g, 0.33 mmol), **Intermediate 200** (50 g, 0.27 mmol) and $K_2CO_3$ (75 mg, 0.54 mmol) in MeCN (3.5 mL) at 85 °C for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-8% MeOH in DCM with 0.5% ammonia in MeOH) to provide the title compound (58 mg). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.52 (d, 1H), 7.31 – 7.03 (m, 6H), 7.00 (dd, 1H), 6.80 (d, 1H), 5.65 – 5.42 (m, 3H), 5.38 – 5.27 (m, 1H), 4.97 (dd, 1H), 4.89 (dd, 1H), 4.86 – 4.82 (m, 1H), 4.81 (t, 1H), 3.78 (t, 2H), 3.44 (s, 3H), 2.82 – 2.60 (m, 3H), 2.55 – 2.35 (m, 5H), 2.24 (s, 6H), 1.98 (s, 3H), 1.88 (q, 2H), 1.61 – 1.54 (m, 2H) – NH not observed.

**Intermediate 202:** Methyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00360]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 201** (58 mg, 0.10 mmol) in DCE (45 mL) and Grubbs II (8 mg, 0.10 mmol) at 40 °C for 18 h. Additional Grubbs II (8 mg, 0.10 mmol) was added at 40 °C for 24 h. Purified by flash chromatography (25 g silica gel, eluting 5-8% MeOH in DCM containing 0.5% ammonia) to provide the title compound (18 mg). LCMS (Method 18): 1.23 min, 590.2 $[M+H]^+$.

**Intermediate 203:** Methyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00361]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 202** (18 mg, 0.03 mmol) and 10% palladium on carbon (3.2 mg) in MeOH (2.5 mL) under a hydrogen atmosphere at RT for 2 h to provide the title compound (17 mg). LCMS (Method 18): 1.25 min, 592.2 $[M+H]^+$.

**Intermediate 204:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2',5-dimethyl-6'-(but-3-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00362]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 127** (0.60 g, 1.39 mmol), $K_2CO_3$ (0.29 g, 2.09 mmol) and 4-bromobut-1-ene (0.16 mL, 1.53 mmol) in MeCN (14 mL) at reflux for 16 h. Extra $K_2CO_3$ (0.38 g, 2.78 mmol) and 4-bromobut-1-ene (0.28 mL, 2.78 mmol) was added and heating continued for 7 h. Extra $K_2CO_3$ (0.38 g, 2.78 mmol) and 4-bromobut-1-ene (0.28 mL, 2.78 mmol) was added and heating continued for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.49 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.05 (t, 1H), 6.89 (dd, 1H), 6.84 (dd, 1H), 6.74 (d, 1H), 6.66 (d, 1H), 5.60 – 5.49 (m, 2H), 5.27 (br s, 1H), 4.91 – 4.84 (m, 2H), 4.04 – 3.91 (m, 2H), 3.78 (t, 2H), 2.80 – 2.60 (m, 2H), 2.17 (d, 2H), 2.13 (s, 3H), 1.94 (s, 3H), 1.30 (s, 9H), 1.06 (t, 3H).

**Intermediate 205:** Ethyl (*S*)-3-amino-3-(2'-(but-3-en-1-yloxy)-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00363]** A suspension of **Intermediate 204** (0.49 g, 1.01 mmol) in 4 M HCl in 1,4-dioxane (0.25 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.43 g). LCMS (Method 18): 1.25 min, 386.1 $[M+H]^+$.

**Intermediate 206:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxyhex-5-enamido)propanoate

**[00364]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 205** (0.33 g, 0.77 mmol), (2*R*-)2-hydroxyhex-5-enoic acid (0.15 g, 0.85 mmol, CAS 612825-60-2), DIPEA (0.40 mL, 2.31 mmol), HOBt (0.10 g, 0.77 mmol) and EDCI (0.15 g, 0.77 mmol) in MeCN (10 mL) at RT for 4 h. Purified by flash chromatography (25 g silica gel, eluting 30 - 100% EtOAc in petroleum ether) to provide the title compound (0.25 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.68 (d, 1H), 7.08 (t, 1H), 6.88 (d, 2H), 6.86 (d, 1H), 6.78 (d, 1H), 5.87 – 5.50 (m, 3H), 4.95 – 4.79 (m, 4H), 4.04 (dd, 1H), 3.98 – 3.91 (m, 2H), 3.89 (t, 2H), 3.48 (br s, 1H), 2.85 – 2.68 (m, 2H), 2.22 – 2.18 (m, 2H), 2.15 (s, 3H), 2.06 – 2.03 (m, 2H), 1.95 (s, 3H), 1.89 – 1.75 (m, 1H), 1.60 – 1.49 (m, 1H), 1.06 (t, 3H).

**Intermediate 207:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)hex-5-enamido)propanoate

**[00365]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 206** (0.11 g, 0.21 mmol), triethylamine (0.06 mL, 0.43 mmol) and methanesulfonyl chloride (25 µL, 0.32 mmol) in DCM (1 mL) at RT for 1 h, to provide the title compound (0.12 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.49 (br s, 1H), 7.11 (t, 1H), 6.89 (dd, 2H), 6.79 (d, 1H), 6.70 (d, 1H), 5.68 – 5.50 (m, 3H), 4.98 – 4.92 (m, 5H), 4.01 – 3.95 (m, 2H), 3.81 (t, 2H), 3.60 (s, 2H), 3.04 (s, 3H), 2.91 – 2.80 (m, 2H), 2.22 (s, 3H), 2.06 – 2.03 (m, 2H), 1.99 (s, 3H), 1.98 – 1.81 (m, 2H), 1.09 (t, 3H).

**Intermediate 208:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)hex-5-enamido)propanoate

**[00366]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 137** (40 mg, 0.24 mmol), **Intermediate 207** (0.11 g, 0.18 mmol) and $K_2CO_3$ (76 mg, 0.55 mmol) in MeCN (2.4 mL) at 85 °C for 18 h. Purified by flash chromatography (25 g silica gel, eluting 2-8% MeOH in DCM with 0.5% ammonia in MeOH) to provide the title compound (25 mg). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.47 (br s, 1H), 7.34 (d, 1H), 7.26 (d, 1H), 7.18 (t, 1H), 6.96 (d, 2H), 6.87 (d, 1H), 6.78 (d, 1H), 6.50 (d, 1H), 5.63 – 5.52 (m, 2H), 5.51 – 5.47 (m, 1H), 5.45 (t, 1H), 4.96 – 4.86 (m, 4H), 3.96 – 3.88 (m, 4H), 2.71 – 2.60 (m, 2H), 2.54 – 2.40 (m, 5H), 2.28 (s, 6H), 2.27 – 2.05 (m, 5H), 1.99 (s, 3H), 1.98 – 1.72 (m, 2H), 1.03 (t, 3H) – NH not observed.

**Intermediate 209:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-6-en-13-yl)acetate

**[00367]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 208** (41 mg, 0.06 mmol) in DCE (30 mL) and Grubbs II (5.4 mg, 6.4 µmol) at 40 °C for 18 h. Purified by flash chromatography (12 g silica gel, eluting 5 - 8% MeOH in DCM containing 0.5% ammonia) to provide the title compound (18 mg). LCMS (Method 18): 2.00 min, 618.3 $[M+H]^+$.

**Intermediate 210:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00368]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 209** (18 mg, 0.03 mmol) and 10% palladium on carbon (3.2 mg) in MeOH (3.1 mL) under a hydrogen atmosphere at RT for 2 h to provide the title compound (14 mg). LCMS (Method 18): 2.02 min, 620.3 $[M+H]^+$.

**Intermediate 211:** Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-hydroxy-4'-6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00369]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 2** (1.51 g, 3.73 mmol), 2-bromo-3,5-dimethylphenol (0.75 g, 3.73 mmol, CAS 125237-08-3), $Na_2CO_3$ (1.19 g, 11.2 mmol) and $Pd(dppf)Cl_2$ (0.14 g, 0.19 mmol) in 1,4-dioxane (30 mL), and water (15 mL) at 80 °C for 16 h. Purified by flash chromatography (40 g silica gel, eluting 10-80% EtOAc in petroleum ether) to provide the title compound (0.45 g). LCMS (Method 4): 1.65 min, 422.1 $[M+Na]^+$.

**Intermediate 212:** Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00370]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 211** (0.45 g, 1.13 mmol), $K_2CO_3$ (0.20 g, 1.46 mmol) and 5-bromopent-1-ene (0.16 mL, 1.35 mmol) in MeCN (10 mL) at reflux for 24 h to provide the title compound (0.47 g). LCMS (Method 4): 2.03 min, 490.0 $[M+Na]^+$.

**Intermediate 213:** Methyl (*S*)-3-amino-3-(2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00371]** A suspension of **Intermediate 212** (0.47 g, 1.00 mmol) in 4 M HCl in 1,4-dioxane (3.75 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure to provide the title compound (0.39 g). LCMS (Method 4): 1.83 min, 368.1 $[M+H]^+$.

**Intermediate 214:** Methyl (*S*)-3-(2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00372]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 213** (0.68 g, 1.68 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.29 g, 2.52 mmol, CAS 413622-10-3), DIPEA (1.17 mL, 6.73 mmol), HOBt (0.25 g, 1.85 mmol) and EDCI (0.48 g, 2.52 mmol) in DMF (2 mL) and MeCN (8 mL) at RT for 18 h. Purified by flash chromatography (40 g silica gel, eluting 5-80% EtOAc in petroleum ether) to provide the title compound (0.33 g). LCMS (Method 11): 2.27 min, 466.0 $[M+H]^+$.

**Intermediate 215:** Methyl (*S*)-3-(2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00373]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 214** (0.30 g, 0.61 mmol), triethylamine (0.17 mL, 1.22 mmol) and methanesulfonyl chloride (0.07 mL, 0.92 mmol) in DCM (3.9 mL) at RT for 2 h, to provide the title compound (0.33 g). LCMS (Method 4): 1.97 min, 544.1 $[M+H]^+$.

**Intermediate 216:** Methyl (*S*)-3-(2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00374]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 137** (0.15 g, 0.90 mmol), **Intermediate 215** (0.33 g, 0.60 mmol) and $K_2CO_3$ (0.17 g, 1.20 mmol) in MeCN (6 mL) at 90 °C for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (94 mg). LCMS (Method 11): 2.45 min, 612.7 $[M-H]^-$.

**Intermediate 217:** Methyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00375]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 216** (0.18 g, 0.29 mmol) in DCE (40 mL) and Grubbs II (25 mg, 0.03 mmol) at 40 °C for 4 h. Purified by flash chromatography (25 g silica gel, eluting 5-65% 9:1 MeOH in DCM containing 0.5% ammonia, in DCM) to provide the title compound (0.11 g). LCMS (Method 11): 2.24 min, 584.6 $[M-H]^-$.

**Intermediate 218:** Methyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00376]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 217** (95 mg, 0.16 mmol) and 10% palladium on carbon (17 mg) in MeOH (2 mL) under a hydrogen atmosphere at RT for 18 h to provide the title compound (80 mg). LCMS (Method 4): 1.93 min, 588.2 $[M+H]^+$.

**Intermediate 219:** (*R*,*E*)-*N*-(5-Bromo-2-fluorobenzylidene)-2-methylpropane-2-sulfinamide

**[00377]** Prepared in an analogous manner to **Intermediate 102** using 5-bromo-2-fluoro-benzaldehyde (2.50 g, 12.3 mmol, CAS 196929-78-9), (*R*)-2-methylpropane-2-sulfinimide (1.64 g, 13.6 mmol, CAS 196929-78-9) and titanium ethoxide (4.21 g, 18.5 mmol) in THF (20 mL) at 40 °C for 2.5 h, to provide the title compound (3.75 g). LCMS (Method 11): 2.10 min, 306.0 $[M+H]^+$.

**Intermediate 220:** Ethyl (*S*)-3-(5-bromo-2-fluorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

**[00378]** Prepared in an analogous manner to **Intermediate 104** using zinc (4.0 g, 61.2 mmol) chlorotrimethylsilane (0.31 mL, 2.45 mmol) and ethyl bromoacetate (3.40 mL, 30.6 mmol) in THF (50 mL) at 60 °C for 1 h, then **Intermediate 219** (3.75 g, 12.2 mmol) in THF (15 mL) at RT for 1.5 h. Purified by flash chromatography (80 g silica gel, eluting 5-80% EtOAc in petroleum ether) to provide the title compound (4.45 g). LCMS (Method 11): 1.94 min, 392.2 $[M-H]^-$.

**Intermediate 221:** Ethyl (*S*)-3-amino-3-(5-bromo-2-fluorophenyl)propanoate hydrochloride

**[00379]** A suspension of **Intermediate 220** (4.45 g, 10.7 mmol) in 4 M HCl in 1,4-dioxane (13.4 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure to provide the title compound (3.21 g). LCMS (Method 11): 1.68 min, 290.4 $[M+H]^+$.

**Intermediate 222:** Ethyl (*S*)-3-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00380]** To a stirred suspension of **Intermediate 221** (3.0 g, 9.19 mmol) and Boc anhydride (2.21 g, 10.1 mmol) in DCM (50 mL) was added triethylamine (1.92 mL, 13.8 mmol) and the mixture stirred for 20 h at RT. The reaction mixture was diluted with DCM and washed with water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (80 g silica gel, eluting 5-35% EtOAc in petroleum ether) to provide the title compound (2.08 g). LCMS (Method 11): 2.12 min, 412.1 $[M+Na]^+$.

**Intermediate 223:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate

**[00381]** Prepared in an analogous manner to **Intermediate 2** using **Intermediate 222** (1.98 g, 5.07 mmol), bis(pinacolato)diboron (1.55 g, 6.09 mmol), potassium acetate (1.24 g, 12.7 mmol) and $Pd(dppf)Cl_2$ (0.37 g, 0.51 mmol) in 1,4-dioxane (20 mL) at 90 °C for 2 h. Purified by flash chromatography (silica gel, eluting 6:1 EtOAc / petroleum ether) to provide the title compound (2.12 g). $^1H$ NMR (400 MHz; $CDCl_3$) δ: 7.69 – 7.67 (m, 1H), 7.65 – 7.60 (m, 1H), 6.95 (dd, 1H), 5.47 – 5.43 (m, 1H), 5.34 – 5.28 (m, 1H), 4.03 – 3.96 (m, 2H), 2.84 – 2.66 (m, 2H), 1.35 (s, 9H), 1.25 (s, 12H), 1.10 (t, 3H).

**Intermediate 224:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00382]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 223** (1.05 g, 2.40 mmol), 2-bromo-3-methylphenol (0.45 g, 2.40 mmol, CAS 22061-78-5), $Na_2CO_3$ (0.64 g, 6.00 mmol) and $Pd(dppf)Cl_2$ (98 mg, 0.12 mmol) in 1,4-dioxane (18 mL), and water (9 mL) at 90 °C for 16 h. Purified by flash chromatography (40 g silica gel, eluting 6:1 EtOAc / petroleum ether) to provide the title compound (0.69 g). LCMS (Method 4): 1.78 min, 440.0 $[M+Na]^+$.

**Intermediate 225:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00383]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 224** (0.69 g, 1.65 mmol), $K_2CO_3$ (0.70 g, 2.15 mmol) and 5-bromopent-1-ene (0.24 mL, 1.98 mmol) in MeCN (15 mL) at reflux for 24 h to provide the title compound (0.70 g). LCMS (Method 4): 2.10 min, 508.1 $[M+Na]^+$.

**Intermediate 226:** Ethyl (*S*)-3-amino-3-(4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00384]** A suspension of **Intermediate 225** (0.70 g, 1.45 mmol) in 4 M HCl in 1,4-dioxane (5.44 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure to provide the title compound (0.61 g). LCMS (Method 12): 1.74 min, 386.3 $[M+H]^+$.

**Intermediate 227:** Ethyl (*S*)-3-(4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00385]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 226** (0.61 g, 1.45 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.25 g, 2.18 mmol, CAS 413622-10-3), DIPEA (1.03 mL, 5.81 mmol), HOBt (0.25 g, 1.74 mmol) and EDCI (0.42 g, 2.18 mmol) in DMF (1.5 mL) and MeCN (7 mL) at RT for 18 h. Purified by flash chromatography (12 g silica gel, eluting 15-55% EtOAc in petroleum ether) to provide the title compound (0.47 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.52 (br d, 1H), 7.13 (t, 1H), 7.11 – 6.96 (m, 3H), 6.80 (d, 1H), 6.71 (d, 1H), 5.73 – 5.55 (m, 3H), 5.12 – 4.99 (m, 2H), 4.85 (dd, 1H), 4.82 (s, 1H), 4.09 (dd, 1H), 4.01 – 3.95 (m, 2H), 3.78 (t, 2H), 2.89 (dd, 1H), 2.79 (dd, 1H), 2.60 – 2.49 (m, 1H), 2.39 – 2.27 (m, 1H), 1.97 (s, 3H), 1.92 – 1.85 (m, 2H), 1.60 – 1.52 (m, 3H), 1.10 (t, 3H).

**Intermediate 228:** Ethyl (*S*)-3-(4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00386]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 227** (0.47 g, 0.98 mmol), triethylamine (0.27 mL, 1.96 mmol) and methanesulfonyl chloride (0.11 mL, 1.47 mmol) in DCM (10 mL) at RT for 1 h, to provide the title compound (0.48 g). LCMS (Method 12): 1.78 min, 562.6 $[M+H]^+$.

**Intermediate 229:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00387]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 137** (0.24 g, 0.86 mmol), **Intermediate 228** (0.37 g, 0.66 mmol) and $K_2CO_3$ (0.27 g, 1.98 mmol) in MeCN (37 mL) at 90 °C for 16 h. Purified by flash chromatography (4 g silica gel, eluting 0-20% 0.1% ammonia in MeOH in DCM) to provide the title compound (0.15 g). LCMS (Method 6): 1.35 min, 632.4 $[M+H]^+$.

**Intermediate 230:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00388]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 229** (0.16 g, 0.25 mmol) in DCE (33 mL) and Grubbs II (21 mg, 0.03 mmol) at 40 °C for 18 h. Additional Grubbs II (21 mg, 0.03 mmol) was added and stirred at 40 °C for 24 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.10 g). LCMS (Method 15): 2.39 min, 604.3 $[M+H]^+$.

**Intermediate 231:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00389]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 230** (0.10 g, 0.10 mmol) and 10% palladium on carbon (11 mg) in ethanol (5 mL) under a hydrogen atmosphere at RT for 5 h to provide the title compound (17 mg). LCMS (Method 11): 2.26 min, 606.5 $[M+H]^+$.

**Intermediate 232:** Ethyl (*S*)-3-amino-3-(5-bromo-3-methyl-2-fluorophenyl)propanoate hydrochloride

**[00390]** A suspension of **Intermediate 123** (3.92 g, 9.60 mmol) in 4 M HCl in 1,4-dioxane (14.4 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure and triturated in petroleum ether to provide the title compound (3.26 g). LCMS (Method 12): 1.41 min, 304.1 $[M+H]^+$.

**Intermediate 233:** Ethyl (*S*)-3-(5-bromo-2-fluoro-3-methylphenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00391]** To a stirred suspension of **Intermediate 232** (3.22 g, 9.45 mmol) and Boc anhydride (2.48 g, 11.3 mmol) in DCM (100 mL) was added DIPEA (2.5 mL, 14.2 mmol) and the mixture stirred for 2 h at RT. The reaction mixture was diluted with DCM and washed with 1 M aqueous HCl, water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (3.11 g). LCMS (Method 4): 1.78 min, 305.8 $[M\text{-}Boc+H]^+$.

**Intermediate 234:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate

**[00392]** Prepared in an analogous manner to **Intermediate 2** using **Intermediate 233** (2.67 g, 6.60 mmol), bis(pinacolato)diboron (2.01 g, 7.93 mmol), potassium acetate (1.62 g, 16.5 mmol) and $Pd(dppf)Cl_2$ (0.48 g, 0.66 mmol) in 1,4-dioxane (43 mL) at 90 °C for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (2.98 g). $^1H$ NMR (400 MHz; $CDCl_3$) δ: 7.59 – 7.52 (m, 2H), 5.47 – 5.43 (m, 1H), 5.34 – 5.28 (m, 1H), 4.10 – 3.99 (m, 2H), 2.90 – 2.66 (m, 2H), 2.25 (s, 3H), 1.42 (s, 9H), 1.32 (s, 12H), 1.18 (t, 3H).

**Intermediate 235:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4,4'-difluoro-2'-hydroxy-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00393]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 234** (3.00 g, 6.65 mmol), 2-bromo-5-fluoro-3-methylphenol (1.50 g, 7.31 mmol, CAS 1807192-21-7), $Na_2CO_3$ (2.11 g, 19.9 mmol) and $Pd(dppf)Cl_2$ (0.36 g, 0.50 mmol) in 1,4-dioxane (180 mL), and water (45 mL) at 85 °C for 20 h. Purified by dry flash chromatography (silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (1.15 g). $^1H$ NMR (400 MHz; $CDCl_3$) δ: 7.08 – 6.92 (m, 2H), 6.54 (d, 2H), 5.81 – 5.64 (m, 1H), 5.42 – 5.21 (m, 1H), 4.09 – 3.96 (m, 2H), 2.86 (d, 2H), 2.30 (s, 3H), 2.02 (s, 3H), 1.41 (s, 9H), 1.18 (t, 3H) – OH not observed.

**Intermediate 236:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4,4'-difluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00394]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 235** (1.15 g, 2.56 mmol), $K_2CO_3$ (0.53 g, 3.84 mmol) and 5-bromopent-1-ene (0.33 mL, 2.81 mmol) in MeCN (32 mL) at reflux for 16 h to provide the title compound (0.86 g). LCMS (Method 4): 2.16 min, 418.1 $[M\text{-}Boc+H]^+$.

**Intermediate 237:** Ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00395]** A suspension of **Intermediate 236** (0.86 g, 1.67 mmol) in 4 M HCl in 1,4-dioxane (5 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.64 g). $^1H$ NMR (400 MHz; $CDCl_3$) δ: 8.97 (br s, 3H), 7.15 (br s, 1H), 7.01 (d, 1H), 6.56 – 6.40 (m, 2H), 5.76 – 5.55 (m, 1H), 5.06 – 4.89 (m, 3H), 4.06 – 3.93 (m, 2H), 3.82 – 3.78 (m, 2H), 3.26 (br d, 1H), 3.07 (br s, 1H), 2.27 (s, 3H), 2.01 (s, 3H), 1.99 – 1.90 (m, 2H), 1.67 – 1.61 (m, 2H), 1.12 (t, 3H).

**Intermediate 238:** Ethyl (*S*)-3-(4,4'-difluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00396]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 237** (0.64 g, 1.41 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.25 g, 2.12 mmol, CAS 413622-10-3), DIPEA (0.98 mL, 5.64 mmol), HOBt (0.21 g, 1.55 mmol) and EDCI (0.41 g, 2.12 mmol) in MeCN (10 mL) at RT for 16 h. Purified by flash chromatography (12 g silica gel, eluting 5-80% EtOAc in petroleum ether) to provide the title compound (0.57 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.58 (br s, 1H), 6.95 – 6.90 (m, 2H), 6.58 – 6.47 (m, 2H), 5.76 – 5.55 (m, 3H), 5.20 – 5.02 (m, 2H), 4.97 – 4.88 (m, 2H), 4.19 – 4.12 (m, 1H), 4.10 – 3.98 (m, 2H), 3.82 (t, 2H), 2.99 – 2.75 (m, 2H), 2.69 – 2.53 (m, 1H), 2.47 – 2.34 (m, 1H), 2.29 (d, 3H), 2.02 (s, 3H), 2.01 – 1.95 (m, 2H), 1.71 – 1.59 (m, 2H), 1.17 (t, 3H) – OH not observed.

**Intermediate 239:** Ethyl (*S*)-3-(4,4'-difluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00397]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 238** (0.57 g, 1.10 mmol), triethylamine (0.31 mL, 2.20 mmol) and methanesulfonyl chloride (0.13 mL, 1.65 mmol) in DCM (7.3 mL) at RT for 1 h, to provide the title compound (0.64 g). LCMS (Method 12): 1.84 min, 592.5 $[M-H]^-$.

**Intermediate 240:** Ethyl (*S*)-3-(4,4'-difluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00398]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 239** (0.50 g, 0.80 mmol), **Intermediate 137** (0.17 g, 1.04 mmol) and $K_2CO_3$ (0.33 g, 2.40 mmol) in MeCN (23 mL) at 90 °C for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-10% 0.1% ammonia in MeOH in DCM) to provide the title compound (0.11 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.54 – 7.37 (m, 1H), 7.31 (d, 1H), 7.27 – 7.23 (m, 1H), 6.95 – 6.89 (m, 2H), 6.63 – 6.46 (m, 3H), 5.75 – 5.52 (m, 4H), 5.03 (d, 1H), 4.98 – 4.89 (m, 3H), 3.97 – 3.87 (m, 2H), 3.83 (t, 2H), 2.85 – 2.65 (m, 3H), 2.63 – 2.44 (m, 5H), 2.42 – 2.23 (m, 9H), 2.00 (s, 3H), 1.99 – 1.90 (m, 2H), 1.65 – 1.53 (m, 2H), 1.11 (t, 3H).

**Intermediate 241:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00399]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 240** (0.11 g, 0.12 mmol) in DCE (79 mL) and Grubbs II (10.6 mg, 0.01 mmol) at 40 °C for 18 h. Additional Grubbs II (10.6 mg, 0.01 mmol) was added and stirred at 40 °C for 24 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% 2 M ammonia MeOH in DCM) and again (12 g

silica gel 8% (0.5% ammonia in MeOH) in DCM) to provide the title compound (48 mg). LCMS (Method 13): 2.33 min, 634.6 $[M-H]^-$.

**Intermediate 242:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00400]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 241** (48 mg, 0.06 mmol) and 10% palladium on carbon (6.1 mg) in MeOH (6.3 mL) under a hydrogen atmosphere at RT for 36 h to provide the title compound (30 mg). LCMS (Method 16): 3.50 min, 638.1 $[M+H]^+$.

**Intermediate 243:** 5-(2-(3-fluoroazetidin-1-yl)ethyl)pyridin-2(1*H*)-one

**[00401]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 136** (0.71 g, 4.59 mmol), 3-fluoroazetidine hydrochloride (0.62 g, 5.51 mmol) and triethylamine (1.28 mL, 9.19 mmol) in MeOH (7 mL), DCM (56 mL) and 4 Å molecular sieves at RT for 2 h, then STAB (2.92 g, 13.8 mmol) at RT for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-20% 1 M ammonia MeOH in DCM) then by reverse phase chromatography (38 g C18 0-50% MeCN in 0.1% aqueous ammonia) to provide the title compound (0.28 g). $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.55 (dd, 1H), 7.27 (d, 1H), 6.52 (d, 1H), 5.21 – 5.02 (m, 1H), 3.69 – 3.56 (m, 2H), 3.29 – 3.17 (m, 2H), 2.71 (t, 2H), 2.47 (t, 2H).

**Intermediate 244:** Methyl (*S*)-3-((*S*)-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00402]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 114** (0.20 g, 0.38 mmol), **Intermediate 243** (74 mg, 0.38 mmol) and $K_2CO_3$ (0.16 g, 1.13 mmol) in MeCN (4 mL) at 85 °C for 18 h. Additional $K_2CO_3$ (0.16 g, 1.13 mmol) was added and heated at 85 °C for 24 h. Purified by flash chromatography (24 g silica gel, eluting 2-10% (0.1% ammonia in MeOH) in DCM) to provide the title compound (69 mg). LCMS (Method 13): 1.66 min, 628.6 $[M-H]^-$.

**Intermediate 245:** Methyl 2-((10*S*,13*S*)-10-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00403]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 244** (69 mg, 0.11 mmol) in DCE (55 mL) and Grubbs II (9.3 mg, 0.01 mmol) at 40 °C for 24 h. Purified by flash chromatography (12 g silica gel, eluting 2-10% 2 M ammonia MeOH in DCM) to provide the title compound (54 mg). LCMS (Method 13): 1.54 min, 600.6 $[M-H]^-$.

**Intermediate 246:** Methyl 2-((10*S*,13*S*)-10-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00404]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 245** (54 mg, 0.08 mmol) and 10% palladium on carbon (8 mg) in MeOH (5 mL) under a hydrogen atmosphere at RT for 40 min. Additional 10% palladium on carbon (8 mg) was added and stirred under a hydrogen atmosphere at RT for 40 min to provide the title compound (48 mg). LCMS (Method 16): 3.17 min, 602.6 $[M-H]^-$.

**Intermediate 247:** (*R*)-5-(2-(3-Fluoropyrrolidin-1-yl)ethyl)pyridin-2(1*H*)-one

**[00405]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 136** (0.82 g, 5.29 mmol), 3-(*R*)-fluoropyrrolidine hydrochloride (0.73 g, 5.82 mmol) and triethylamine (0.88 mL, 6.34 mmol) in MeOH (7 mL), DCM (56 mL) and 4 Å molecular sieves at RT for 3 h, then STAB (3.36 g, 15.0 mmol) at RT for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-20% 1 M ammonia MeOH in DCM) then by reverse phase chromatography (38 g C18, 0-50% MeCN in 0.1% aqueous ammonia) to provide the title compound (0.28 g). $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.57 (dd, 1H), 7.31 (dd, 1H), 6.52 (dd, 1H), 5.29 – 5.06 (m, 1H), 3.06 – 2.89 (m, 2H), 2.77 – 2.58 (m, 5H), 2.51 – 2.40 (m, 1H), 2.30 – 2.10 (m, 1H), 2.10 – 1.92 (m, 1H).

**Intermediate 248:** Methyl (*S*)-3-((*S*)-2-(5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00406]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 114** (0.20 g, 0.38 mmol), **Intermediate 247** (79 mg, 0.38 mmol) and $K_2CO_3$ (0.16 g, 1.13 mmol) in MeCN (4 mL) at 85 °C for 18 h. Purified by flash chromatography (24 g silica gel, eluting 2-10% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.15 g). LCMS (Method 13): 1.71 min, 644.6 $[M+H]^+$.

**Intermediate 249:** Methyl 2-((10*S*,13*S*)-10-(5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00407]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 248** (0.15 g, 0.11 mmol) in DCE (0.11 L) and Grubbs II (19.1 mg, 0.02 mmol) at 40 °C for 18 h. Additional Grubbs II (9.6 mg, 0.01 mmol) was added and heated at 40 °C for 6 h. Purified by flash chromatography (24 g silica gel, eluting 2-8% 2 M ammonia MeOH in DCM) to provide the title compound (91 mg). LCMS (Method 16): 3.12 min, 614.7 $[M-H]^-$.

**Intermediate 250:** Methyl 2-((10*S*,13*S*)-10-(5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00408]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 249** (91 mg, 0.14 mmol) and 10% palladium on carbon (14.8 mg) in MeOH (8 mL) under a hydrogen atmosphere at RT for 40 min. Additional 10% palladium on carbon (14.8 mg) was added and stirred under a hydrogen atmosphere at RT for 40 min to provide the title compound (72 mg). LCMS (Method 16): 4.33 min, 616.6 $[M-H]^-$.

**Intermediate 251:** 5-(2-(3-Methoxyazetidin-1-yl)ethyl)pyridin-2(1*H*)-one

**[00409]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 136** (0.78 g, 5.05 mmol), 3-methoxyazetidine hydrochloride (0.69 g, 5.55 mmol) and triethylamine (1.41 mL, 10.1 mmol) in MeOH (7.7 mL), DCM (62 mL) and 4 Å molecular sieves at RT for 2 h, then STAB (3.21 g, 15.2 mmol) at RT for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-20% 1 M ammonia MeOH in DCM) then by reverse phase chromatography (38 g C18, 0-50% MeCN in 0.1% aqueous ammonia) to provide the title compound (0.35 g). $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.54 (dd, 1H), 7.26 (d, 1H), 6.51 (d, 1H), 4.10 – 3.99 (m, 1H), 3.58 (dd, 2H), 3.24 (s, 3H), 3.02 – 2.94 (m, 2H), 2.67 (t, 2H), 2.46 (t, 2H).

**Intermediate 252:** Methyl (*S*)-3-((*S*)-2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00410]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 114** (0.20 g, 0.38 mmol), **Intermediate 251** (79 mg, 0.38 mmol) and $K_2CO_3$ (0.16 g, 1.13 mmol) in MeCN (4 mL) at 85 °C for 18 h. Purified by flash chromatography (24 g silica gel, eluting 4-10% (0.1% ammonia MeOH) in DCM) to provide the title compound (97 mg). LCMS (Method 13): 1.70 min, 640.6 $[M-H]^-$.

**Intermediate 253:** Methyl 2-((10*S*,13*S*)-10-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00411]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 252** (97 mg, 0.14 mmol) in DCE (75 mL) and Grubbs II (12.1 mg, 0.02 mmol) at 40 °C for 18 h. Additional Grubbs II (6 mg, 0.01 mmol) was added and heated at 40 °C for 6 h. Purified by flash chromatography (24 g silica gel, eluting 2-8% 2 M ammonia MeOH in DCM) to provide the title compound (42 mg). LCMS (Method 16): 3.12 min, 612.6 $[M-H]^-$.

**Intermediate 254:** Methyl 2-((10*S*,13*S*)-10-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00412]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 253** (42 mg, 0.06 mmol) and 10% palladium on carbon (6.4 mg) in MeOH (5 mL) under a hydrogen atmosphere at RT for 40 min. Additional 10% palladium on carbon (6.4 mg) was added and stirred under a hydrogen atmosphere at RT for 40 min to provide the title compound (40 mg). LCMS (Method 16): 3.18 min, 616.2 $[M+H]^+$.

**Intermediate 255:** (*E*)-5-(2-Ethoxyvinyl)-2-methoxy-4-(trifluoromethyl)pyridine

**[00413]** Prepared in an analogous manner to **Intermediate 197** using 5-bromo-4-trifluoromethyl-2-methoxypyridine (2.25 g, 8.79 mmol, CAS 688047-09-8), 2-[(*E*)-2-ethoxyvinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.09 g, 10.6 mmol), $K_2CO_3$ (3.64 g, 26.4 mmol) and $Pd(PPh_3)_4$ (0.51 g, 0.44 mmol) in 1,4-dioxane (27 mL) and water (6 mL) at 100 °C for 3 h. Purified by flash chromatography (40 g silica gel, eluting 0-20% 1 M ammonia MeOH in DCM) then by reverse phase chromatography (40 g silica gel, 0-60% MeCN in petroleum ether) to provide the title compound (1.81 g). LCMS (Method 4): 1.72 min, 247.9 $[M+H]^+$.

**Intermediate 256:** 2-(6-Methoxy-4-(trifluoromethyl)pyridin-3-yl)ethane-1,1-diol

**[00414]** A solution of **Intermediate 255** (0.50 g, 1.82 mmol) in TFA (2.2 mL) was stirred at 20 °C for 2 h. The mixture was cooled and concentrated under reduced pressure to provide the title compound (0.43 g). $^1$H NMR (400 MHz; $CD_3OD$) δ: 8.26 (s, 1H), 7.02 (s, 1H), 4.62 (t, 1H), 3.95 (s, 3H), 2.96 (dq, 2H).

**Intermediate 257:** 2-(6-Methoxy-4-(trifluoromethyl)pyridin-3-yl)-*N*,*N*-dimethylethan-1-amine

**[00415]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 256** (0.43 g, 1.82 mmol), dimethylamine (2 M in THF, 1.82 mL, 3.63 mmol), triethylamine (0.425 mL, 1.82 mmol) in DCM (15 mL) and 4 Å molecular sieves at RT for 16 h, then STAB (0.77 g, 3.63 mmol) at RT for 6 h. Purified by flash chromatography (12 g silica gel, eluting 0-6% MeOH in DCM) then by flash chromatography (20 g C18, 0–100% MeCN in 0.1 M aqueous ammonia) to provide the title compound (0.29 g). LCMS (Method 4): 1.48 min, 249.0 $[M+H]^+$.

**Intermediate 258:** 5-(2-(Dimethylamino)ethyl)-4-(trifluoromethyl)pyridin-2(1*H*)-one

**[00416]** A solution of **Intermediate 257** (0.29 g, 1.17 mmol) in 33% HBr in AcOH (4.03 mL, 23.4 mmol) was stirred at 85 °C for 1 h. The mixture was cooled and concentrated under reduced pressure. The crude product was purified by catch and release chromatography (1 g

SCX, eluting MeOH followed by 1 M ammonia in MeOH) to provide the title compound (0.15 g). LCMS (Method 4): 1.00 min, 234.9 $[M+H]^+$.

**Intermediate 259:** Methyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00417]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 114** (0.23 g, 0.39 mmol), **Intermediate 258** (92 mg, 0.39 mmol) and $K_2CO_3$ (0.16 g, 1.18 mmol) in MeCN (3 mL) at 85 °C for 18 h. Purified by flash chromatography (24 g silica gel, eluting 2-8% (0.1% ammonia MeOH) in DCM) and again (24 g silica gel, eluting 2.5% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.10 g). LCMS (Method 13): 1.70 min, 666.7 $[M-H]^-$.

**Intermediate 260:** Methyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00418]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 259** (0.10 g, 0.15 mmol) in DCE (75 mL) and Grubbs II (12.7 mg, 0.02 mmol) at 40 °C for 18 h. Additional Grubbs II (12.7 mg, 0.02 mmol) was added and heated at 40 °C for 6 h. Purified by flash chromatography (24 g silica gel, eluting 0-10% 2 M ammonia MeOH in DCM) to provide the title compound (44 mg). LCMS (Method 16): 3.18 min, 638.5 $[M-H]^-$.

**Intermediate 261:** Methyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00419]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 260** (44 mg, 0.06 mmol) and 10% palladium on carbon (6.5 mg) in MeOH (3 mL) under a hydrogen atmosphere at RT for 1 h. Purified flash chromatography (24 g silica gel, eluting 0-10% 2 M ammonia MeOH in DCM) to provide the title compound (35 mg). LCMS (Method 7): 1.59 min, 642.2 $[M+H]^+$.

**Intermediate 262:** 5-(2-(Azetidin-1-yl)ethyl)pyridin-2(1*H*)-one

**[00420]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 136** (0.78 g, 5.05 mmol), azetidine (0.68 mL, 10.1 mmol), triethylamine (1.41 mL, 10.1 mmol) in DCM (15 mL) and 4 Å molecular sieves at RT for 2 h, then STAB (3.21 g, 15.2 mmol) at RT for 2 h. Purified by flash chromatography (40 g silica gel, eluting 0-20% MeOH in DCM) then by flash chromatography (38 g C18, 0–50% MeCN in 0.1 M aqueous ammonia) to provide the title compound (0.39 g). $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.53 (dd, 1H), 7.26 (d, 1H), 6.52 (d, 1H), 3.25 (t, 4H), 2.62 (t, 2H), 2.44 (t, 2H), 2.14 – 2.07 (m, 2H).

**Intermediate 263:** (*R*,*E*)-*N*-(3-Bromo-5-methylbenzylidene)-2-methylpropane-2-sulfinamide

**[00421]** Prepared in an analogous manner to **Intermediate 102** using 5-bromo-3-methyl-benzaldehyde (2.50 g, 12.6 mmol, CAS 188813-04-9), (*R*)-2-methylpropane-2-sulfinimide (1.67 g, 13.8 mmol, CAS 196929-78-9) and titanium ethoxide (4.30 g, 18.8 mmol) in THF (20 mL) at 40 °C for 2.5 h, to provide the title compound (3.65 g). LCMS (Method 11): 2.22 min, 302.1 $[M+H]^+$.

**Intermediate 264:** Ethyl (*S*)-3-(5-bromo-3-methylphenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

**[00422]** Prepared in an analogous manner to **Intermediate 104** using zinc (3.9 g, 60.4 mmol) chlorotrimethylsilane (0.31 mL, 2.42 mmol) and ethyl bromoacetate (3.35 mL, 30.2 mmol) in THF (72 mL) at 60 °C for 1 h, then **Intermediate 263** (3.65 g, 12.1 mmol) in THF (72 mL) at RT for 1.5 h. Purified by flash chromatography (80 g silica gel, eluting 5-80% EtOAc in petroleum ether) to provide the title compound (3.98 g). LCMS (Method 11): 2.05 min, 390.1 $[M+H]^+$.

**Intermediate 265:** Ethyl (*S*)-3-amino-3-(3-bromo-5-methylphenyl)propanoate hydrochloride

**[00423]** A suspension of **Intermediate 264** (3.98 g, 10.2 mmol) in 4 M HCl in 1,4-dioxane (5 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure to provide the title compound (2.95 g). LCMS (Method 11): 1.79 min, 286.4 $[M+H]^+$.

**Intermediate 266:** Ethyl (*S*)-3-(3-bromo-5-methylphenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00424]** To a stirred suspension of **Intermediate 265** (2.80 g, 8.68 mmol) and Boc anhydride (2.08 g, 9.55 mmol) in DCM (85 mL) was added triethylamine (1.82 mL, 13.0 mmol) and the mixture stirred for 20 h at RT. The reaction mixture was diluted with DCM and washed with water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (80 g silica gel, eluting 5-35% EtOAc in petroleum ether) to provide the title compound (1.95 g). LCMS (Method 11): 2.21 min, 408.1 $[M+Na]^+$.

**Intermediate 267:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate

**[00425]** Prepared in an analogous manner to **Intermediate 2** using **Intermediate 266** (1.85 g, 4.79 mmol), bis(pinacolato)diboron (1.46 g, 5.75 mmol), and $Pd(dppf)Cl_2$ (0.35 g, 0.48 mmol) in 1,4-dioxane (19 mL) at 90 °C for 16 h. Purified by dry flash chromatography (silica gel, eluting 1:6 EtOAc / petroleum ether) to provide the title compound (2.06 g). $^1H$ NMR (400

MHz; $CDCl_3$) δ: 7.46 – 7.44 (m, 2H), 7.14 (s, 1H), 5.29 (br s, 1H), 5.04 – 4.92 (br m, 1H), 4.07 – 3.92 (m, 2H), 2.83 – 2.65 (m, 2H), 2.26 (s, 3H), 1.35 (s, 9H), 1.26 (s, 12H), 1.11 (t, 3H).

**Intermediate 268:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-hydroxy-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00426]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 267** (1.00 g, 2.31 mmol), 2-bromo-3-methylphenol (0.43 g, 7.31 mmol, CAS 22061-78-5), $Na_2CO_3$ (0.61 g, 5.77 mmol) and Pd(dppf)$Cl_2$ (94 mg, 0.12 mmol) in 1,4-dioxane (88 mL), and water (18 mL) at 90 °C for 20 h. Purified by dry flash chromatography (silica gel, eluting 1:5 EtOAc / petroleum ether) to provide the title compound (0.61 g). LCMS (Method 4): 1.82 min, 436.0 $[M+Na]^+$.

**Intermediate 269:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00427]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 268** (0.61 g, 1.47 mmol), $K_2CO_3$ (0.62 g, 1.91 mmol) and 5-bromopent-1-ene (0.21 mL, 1.77 mmol) in MeCN (15 mL) at reflux for 16 h to provide the title compound (0.60 g). LCMS (Method 4): 2.13 min, 504.1 $[M+Na]^+$.

**Intermediate 270:** Ethyl (*S*)-3-amino-3-(2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00428]** A suspension of **Intermediate 269** (0.60 g, 1.24 mmol) in 4 M HCl in 1,4-dioxane (4.6 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure to provide the title compound (0.51 g). LCMS (Method 12): 1.78 min, 404.3 $[M+Na]^+$.

**Intermediate 271:** Ethyl (*S*)-3-(2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00429]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 270** (0.52 g, 1.23 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.22 g, 1.85 mmol, CAS 413622-10-3), DIPEA (0.88 mL, 4.93 mmol), HOBt (0.20 g, 1.48 mmol) and EDCI (0.35 g, 1.85 mmol) in MeCN (6 mL) and DMF (1 mL) at RT for 16 h. Purified by flash chromatography (12 g silica gel, eluting 15-55% EtOAc in petroleum ether) to provide the title compound (0.41 g). $^1H$ NMR (400 MHz; $CDCl_3$) δ: 7.36 (d, 1H), 7.11 (t, 1H), 6.98 (s, 1H), 6.87 (d, 2H), 6.80 (d, 1H), 6.71 (d, 1H), 5.79 – 5.56 (m, 2H), 5.42 – 5.32 (m, 1H), 5.15 – 5.04 (m, 2H), 4.90 – 4.79 (m, 2H), 4.10 (dd, 1H), 4.00 (q, 2H), 3.79 (t, 2H), 2.86 (dd, 1H), 2.75 (dd, 1H), 2.58 (dt, 1H), 2.29 (s, 3H), 1.98 (s, 3H), 1.90 (q, 2H), 1.61 – 1.52 (m, 2H), 1.10 (t, 3H) – OH and NH not observed.

**Intermediate 272:** Ethyl (*S*)-3-(2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00430]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 271** (0.41 g, 0.86 mmol), triethylamine (0.24 mL, 1.72 mmol) and methanesulfonyl chloride (0.10 mL, 1.29 mmol) in DCM (1 mL) at RT for 2 h, to provide the title compound (0.45 g). LCMS (Method 12): 1.81 min, 559.4 $[M+H]^+$.

**Intermediate 273:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00431]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 272** (0.37 g, 0.66 mmol), **Intermediate 262** (0.14 g, 0.80 mmol) and $K_2CO_3$ (0.26 g, 1.99 mmol) in MeCN (7.4 mL) at 85 °C for 30 h. Purified by flash chromatography (12 g silica gel, eluting 0-20% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.10 g). LCMS (Method 6): 1.34 min, 640.5 $[M+H]^+$.

**Intermediate 274:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(azetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00432]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 273** (0.10 g, 0.15 mmol) in DCE (75 mL) and Grubbs II (13 mg, 0.02 mmol) at 40 °C for 18 h. Additional Grubbs II (13 mg, 0.02 mmol) was added and heated at 40 °C for 24 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% 2 M ammonia MeOH in DCM) to provide the title compound (13 mg). LCMS (Method 13): 1.63 min, 612.5 $[M+H]^+$.

**Intermediate 275:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(azetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00433]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 274** (13 mg, 0.02 mmol) and 10% palladium on carbon (2 mg) in MeOH (1.5 mL) under a hydrogen atmosphere at RT for 1 h. Additional 10% palladium on carbon (2 mg) was added and stirred under a hydrogen atmosphere at RT for 2 h. Purified flash chromatography (4 g silica gel, eluting 0-10% 2 M ammonia MeOH in DCM) to provide the title compound (10 mg). LCMS (Method 13): 1.65 min, 614.5 $[M+H]^+$.

**Intermediate 276:** (*R*)-3-Fluoro-5-(2-(3-fluoropyrrolidin-1-yl)ethyl)-2-methoxypyridine

**[00434]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 198** (0.17 g, 1.01 mmol), (R)-3-fluoropyrrolidine hydrochloride (0.15 g, 1.22 mmol, CAS 136725-55-8), triethylamine (0.28 mL, 2.03 mmol) in DCM (6.6 mL) and 4 Å molecular sieves at RT for 5 h, then STAB (0.43 g, 2.03 mmol) at RT for 18 h. Purified by reverse phase chromatography (20 g C18, 5-70% MeCN in 0.1% aqueous ammonia) to provide the title compound (70 mg). LCMS (Method 11): 0.86 min, 242.9 $[M+H]^+$.

**Intermediate 277:** (*R*)-3-Fluoro-5-(2-(3-fluoropyrrolidin-1-yl)ethyl)pyridin-2(1*H*)-one

**[00435]** A solution of **Intermediate 276** (70 mg, 0.29 mmol) in 33% HBr in AcOH (1.0 mL, 5.78 mmol) was stirred at 85 °C for 2 h. The mixture was cooled and concentrated under reduced pressure. The crude product was purified by reverse-phase chromatography (20 g C18, 2-60% MeCN in 0.1% aqueous ammonia)to provide the title compound (53 mg). LCMS (Method 7): 0.98 min, 228.9 $[M+H]^+$.

**Intermediate 278:** Ethyl (*S*)-3-(4,4'-difluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00436]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 239** (0.27 g, 0.45 mmol), **Intermediate 277** (98 mg, 0.43 mmol) and $K_2CO_3$ (0.18 g, 1.29 mmol) in MeCN (3 mL) at 85 °C for 30 h. Purified by flash chromatography (24 g silica gel, eluting 0-10% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.11 g). LCMS (Method 11): 1.84 min, 724.7 $[M-H]^-$.

**Intermediate 279:** Ethyl 2-((10*S*,13*S*)-$1^4$,$2^4$-difluoro-10-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00437]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 278** (0.11 g, 0.15 mmol) in DCE (70 mL) and Grubbs II (13 mg, 0.02 mmol) at 40 °C for 5 h. Additional Grubbs II (13 mg, 0.02 mmol) was added and heated at 40 °C for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% 2 M ammonia MeOH in DCM) to provide the title compound (85 mg). LCMS (Method 11): 2.27 min, 698.5 $[M+H]^+$.

**Intermediate 280:** Ethyl 2-((10*S*,13*S*)-$1^4$,$2^4$-difluoro-10-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00438]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 279** (85 mg, 0.12 mmol) and 10% palladium on carbon (13 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 8 h, to provide the title compound (80 mg). LCMS (Method 15): 2.41 min, 700.3 $[M+H]^+$.

**Intermediate 281:** 3-Fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-methoxypyridine

**[00439]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 198** (1.29 g, 7.60 mmol), 3-fluoroazetidine hydrochloride (1.02 g, 9.12 mmol, CAS 617718-46-4), triethylamine (2.12 mL, 15.2 mmol) in DCM (40 mL) and 4 Å molecular sieves at RT for 6 h,

then STAB (3.22 g, 15.2 mmol) at RT for 18 h. Purified by flash chromatography (25 g silica gel, 0-4% 2 M ammonia MeOH in DCM) to provide the title compound (0.49 g). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, 1H), 7.18 (dd, 1H), 5.27 – 5.03 (m, 1H), 3.96 (s, 3H), 3.96 – 3.83 (m, 2H), 3.35 – 3.18 (m, 2H), 2.79 (t, 2H), 2.64 (t, 2H).

**Intermediate 282:** 3-Fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)pyridin-2(1*H*)-one

**[00440]** A solution of **Intermediate 281** (0.53 g, 2.33 mmol) in 33% HBr in AcOH (6.0 mL, 35.0 mmol) was stirred at 85 °C for 2 h. The mixture was cooled and concentrated under reduced pressure. The crude product was purified by catch and release chromatography (10 g SCX, eluting MeOH followed by 1 M ammonia in MeOH) then by reverse-phase chromatography (32 g C18, 5-50% MeCN in 0.1% aqueous ammonia) to provide the title compound (0.22 g). LCMS (Method 4): 0.77 min, 214.9 $[M+H]^+$.

**Intermediate 283:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2'-hydroxy-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00441]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 234** (3.00 g, 6.65 mmol), 2-bromo-3,5-dimethylphenol (1.34 g, 6.65 mmol, CAS 125237-08-3), $Na_2CO_3$ (2.11 g, 19.9 mmol) and Pd(dppf)$Cl_2$ (0.24 g, 0.33 mmol) in 1,4-dioxane (183 mL), and water (46 mL) at 85 °C for 20 h. Purified by dry flash chromatography (silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (1.56 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.10 – 6.95 (m, 2H), 6.66 (s, 2H), 5.73 (br s, 1H), 5.34 (br s, 1H), 4.07 (d, 2H), 2.86 (d, 2H), 2.30 (s, 6H), 2.00 (s, 3H), 1.41 (s, 9H), 1.17 (t, 3H) – OH not observed.

**Intermediate 284:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2',4',5-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00442]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 283** (1.56 g, 3.50 mmol), $K_2CO_3$ (0.73 g, 5.25 mmol) and 5-bromopent-1-ene (0.46 mL, 3.85 mmol) in MeCN (43 mL) at reflux for 16 h to provide the title compound (1.06 g). LCMS (Method 7): 2.79 min, 414.1 $[M-Boc+H]^+$.

**Intermediate 285:** Ethyl (*S*)-3-amino-3-(4-fluoro-2',4',5-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00443]** A suspension of **Intermediate 284** (1.06 g, 2.05 mmol) in 4 M HCl in 1,4-dioxane (5.1 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.85 g). LCMS (Method 7): 1.74 min, 414.2 $[M+H]^+$.

**Intermediate 286:** Ethyl (*S*)-3-(4-fluoro-2',4',5-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00444]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 285** (0.85 g, 1.89 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.33 g, 2.83 mmol, CAS 413622-10-3), DIPEA (1.31 mL, 7.54 mmol), HOBt (0.28 g, 2.08 mmol) and EDCI (0.54 g, 2.83 mmol) in MeCN (16 mL) at RT for 16 h. Purified by flash chromatography (25 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.64 g). LCMS (Method 7): 2.48 min, 512.1 $[M+H]^+$.

**Intermediate 287:** Ethyl (*S*)-3-(4-fluoro-2',4',5-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00445]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 286** (0.25 g, 0.48 mmol), triethylamine (0.13 mL, 0.96 mmol) and methanesulfonyl chloride (0.06 mL, 0.72 mmol) in DCM (3.2 mL) at 0 °C for 1 h, to provide the title compound (0.28 g). LCMS (Method 4): 1.96 min, 590.1 $[M+H]^+$.

**Intermediate 288:** Ethyl (*S*)-3-(4-fluoro-2',4',5-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00446]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 287** (0.28 g, 0.47 mmol), **Intermediate 282** (0.11 g, 0.52 mmol) and $K_2CO_3$ (0.20 g, 1.42 mmol) in MeCN (5.6 mL) at 85 °C for 18 h. Purified by flash chromatography (25 g silica gel, eluting 5-8% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.14 g). LCMS (Method 3): 1.42 min, 708.3 $[M+H]^+$.

**Intermediate 289:** Ethyl 2-((10*S*,13*S*)-$1^4$-fluoro-10-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00447]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 288** (0.14 g, 0.20 mmol) in DCE (96 mL) and Grubbs II (17 mg, 0.02 mmol) at 40 °C for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-8% (0.5% ammonia MeOH) in DCM) to provide the title compound (82 mg). LCMS (Method 4): 1.84 min, 680.3 $[M+H]^+$.

**Intermediate 290:** Ethyl 2-((10*S*,13*S*)-$1^4$-fluoro-10-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00448]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 289** (82 mg, 0.12 mmol) and 10% palladium on carbon (1.3 mg) in ethanol (12 mL) under a hydrogen atmosphere at RT for 2 h. Additional 10% palladium on carbon (13 mg) was added and stirred under a hydrogen atmosphere at RT for 3 h. Purified by reverse-phase chromatography (55 g

C18, eluting 5-80% MeCN in 0.1% aqueous formic acid) to provide the title compound (22 mg). LCMS (Method 7): 1.65 min, 682.2 $[M+H]^+$.

**Intermediate 291:** Ethyl (*S*)-3-(4,4'-difluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00449]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 239** (0.28 g, 0.47 mmol), **Intermediate 282** (0.10 g, 0.47 mmol) and $K_2CO_3$ (0.13 g, 0.93 mmol) in MeCN (5 mL) at 90 °C for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-4% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.10 g). LCMS (Method 4): 1.93 min, 712.2 $[M+H]^+$.

**Intermediate 292:** Ethyl 2-((10*S*,13*S*)-$1^4$,$2^4$-difluoro-10-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00450]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 291** (0.10 g, 0.14 mmol) in DCE (20 mL) and Grubbs II (12 mg, 0.01 mmol) at 40 °C for 24 h. Additional Grubbs II (6 mg, 0.01 mmol) was added and stirred at 40 °C for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-4% (0.1% ammonia MeOH) in DCM) to provide the title compound (62 mg). LCMS (Method 4): 1.78 min, 684.2 $[M+H]^+$.

**Intermediate 293:** Ethyl 2-((10*S*,13*S*)-$1^4$,$2^4$-difluoro-10-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00451]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 292** (62 mg, 0.09 mmol) and 10% palladium on carbon (9.7 mg) in MeOH (2 mL) under a hydrogen atmosphere at RT for 18 h, to provide the title compound (47 mg). LCMS (Method 4): 1.81 min, 686.2 $[M+H]^+$.

**Intermediate 294:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4-fluoro-2',4',5-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00452]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 287** (0.13 g, 0.22 mmol), **Intermediate 258** (52 mg, 0.22 mmol) and $K_2CO_3$ (92 mg, 0.66 mmol) in MeCN (2.7 mL) at 90 °C for 16 h. Purified by flash chromatography (25 g silica gel, eluting 0-6% (0.1% ammonia MeOH) in DCM) to provide the title compound (60 mg). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.52 (s, 1H), 7.36 (d, 1H), 6.92 – 6.85 (m, 2H), 6.79 (s, 1H), 6.62 (s, 1H), 6.52 (d, 1H), 5.67 – 5.46 (m, 4H), 5.00 – 4.95 (m, 1H), 4.91 – 4.82 (m, 3H), 3.92 – 3.83 (m, 2H), 3.77

(t, 2H), 2.78 – 2.69 (m, 3H), 2.60 (t, 2H), 2.54 – 2.44 (m, 2H), 2.43 – 2.33 (m, 2H), 2.26 (s, 3H), 2.24 – 2.22 (m, 5H), 2.21 – 2.19 (m, 3H), 1.94 – 1.89 (m, 5H), 1.61 – 1.57 (m, 2H), 1.03 (t, 3H).

**Intermediate 295:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00453]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 294** (60 mg, 0.08 mmol) in DCE (39 mL) and Grubbs II (7 mg, 8.0 µmol) at 40 °C for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-8% (0.1% ammonia MeOH) in DCM) to provide the title compound (34 mg). LCMS (Method 18): 1.35 min, 700.3 $[M+H]^+$.

**Intermediate 296:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00454]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 295** (44 mg, 0.09 mmol) and 10% palladium on carbon (4.5 mg) in ethanol (4.9 mL) under a hydrogen atmosphere at RT for 2 h. Purified by reverse-phase chromatography (20 g C18, eluting 10-70% MeCN in 0.1% aqueous formic acid) to provide the title compound (26 mg). LCMS (Method 18): 1.35 min, 702.3 $[M+H]^+$.

**Intermediate 297:** 2-Methoxy-5-(2-(3-methoxyazetidin-1-yl)ethyl)-4-(trifluoromethyl)pyridine

**[00455]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 256** (1.2 g, 5.06 mmol), 3-methoxyazetidine hydrochloride (0.75 g, 6.07 mmol), triethylamine (0.85 mL, 6.07 mmol) in DCM (25 mL) and 4 Å molecular sieves at RT for 16 h, then STAB (2.14 g, 10.1 mmol) at RT for 6 h. Purified by flash chromatography (12 g silica gel, eluting 0-6% MeOH in DCM) then by reverse phase chromatography (20 g C18, 0–100% MeCN in 0.1 M aqueous ammonia) to provide the title compound (0.48 g). LCMS (Method 22): 1.41 min, 291.0 $[M+H]^+$.

**Intermediate 298:** 5-(2-(3-Methoxyazetidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-2(1*H*)-one

**[00456]** To a solution of **Intermediate 297** (0.36 g, 1.24 mmol) in DCM (7 mL) and chloroform (7 mL) was added iodotrimethylsilane (0.21 mL, 1.49 mmol) was stirred at 40 °C for 18 h. The mixture was concentrated under reduced pressure. This was dissolved in DCM (7 mL), chloroform (7 mL) and MeCN (5 mL) then iodotrimethylsilane (0.21 mL, 1.49 mmol) was added and stirred at 40 °C for 4 h. The mixture was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography (38 g C18, 0–30% MeCN in 0.1 M aqueous ammonia) to provide the title compound (0.13 g). LCMS (Method 22): 1.04 min, 276.9 $[M+H]^+$.

**Intermediate 299:** Ethyl (*S*)-3-(4,4'-difluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00457]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 239** (0.28 g, 0.47 mmol), **Intermediate 298** (0.13 g, 0.42 mmol) and $K_2CO_3$ (0.18 g, 1.27 mmol) in MeCN (3 mL) at 85 °C for 16 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.12 g). LCMS (Method 23): 1.94 min, 774.5 $[M+H]^+$.

**Intermediate 300:** Ethyl 2-((10*S*,13*S*)-$1^4$,$2^4$-difluoro-10-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00458]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 299** (0.13 g, 0.16 mmol) in DCE (70 mL) and Grubbs II (14 mg, 0.10 mmol) at 40 °C for 18 h. Additional Grubbs II (14 mg, 0.10 mmol) were added and stirred at 40 °C for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.11 g). LCMS (Method 24): 3.55 min, 746.2 $[M+H]^+$.

**Intermediate 301:** Ethyl 2-((10*S*,13*S*)-$1^4$,$2^4$-difluoro-10-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00459]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 300** (0.11 g, 0.14 mmol) and 10% palladium on carbon (15 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 2 h. Purified by reverse-phase chromatography (38 g C18, eluting 30-80% MeCN in 0.1% aqueous formic acid) to provide the title compound (34 mg). LCMS (Method 18): 1.34 min, 748.3 $[M+H]^+$.

**Intermediate 302:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4,4'-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00460]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 235** (3.50 g, 7.50 mmol), $K_2CO_3$ (1.55 g, 11.3 mmol) and 4-bromobut-1-ene (0.84 mL, 8.25 mmol) in MeCN (75 mL) at reflux for 16 h. Additional $K_2CO_3$ (1.55 g, 11.3 mmol) and 4-bromobut-1-ene (0.84 mL, 8.25 mmol) were added and refluxed for 26 h, to provide the title compound (2.80 g). LCMS (Method 23): 2.56 min, 404.3 $[M-Boc+H]^+$.

**Intermediate 303:** Ethyl (*S*)-3-amino-3-(2'-(but-3-en-1-yloxy)-4,4'-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00461]** A suspension of **Intermediate 302** (2.8 g, 5.56 mmol) in 4 M HCl in 1,4-dioxane (5 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (2.55 g). LCMS (Method 23): 1.61 min, 404.3 $[M+H]^+$.

**Intermediate 304:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4,4'-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxyhex-5-enamido)propanoate

**[00462]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 303** (2.55 g, 5.51 mmol), (2*R*)-2-hydroxyhex-5-enoic acid (1.08 g, 8.26 mmol, CAS 612825-60-2), DIPEA (3.84 mL, 22.0 mmol), HOBt (0.82 g, 6.06 mmol) and EDCI (1.58 g, 8.26 mmol) in MeCN (46 mL) at RT for 16 h. Purified by flash chromatography (40 g silica gel, eluting 5-80% EtOAc in petroleum ether) to provide the title compound (1.42 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.49 (d, 1H), 6.95 – 6.87 (m, 2H), 6.57 (dd, 1H), 6.49 (dd, 1H), 5.88 – 5.77 (m, 1H), 5.71 – 5.59 (m, 2H), 5.04 – 4.94 (m, 4H), 4.18 – 4.10 (m, 1H), 4.09 – 4.01 (m, 2H), 3.86 (t, 2H), 2.98 – 2.81 (m, 2H), 2.37 – 2.24 (m, 6H), 2.20 – 2.10 (m, 2H), 2.01 (s, 3H), 1.96 – 1.86 (m, 1H), 1.74 – 1.64 (m, 1H), 1.17 (t, 3H).

**Intermediate 305:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4,4'-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)hex-5-enamido)propanoate

**[00463]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 304** (0.23 g, 0.45 mmol), triethylamine (0.13 mL, 0.91 mmol) and methanesulfonyl chloride (0.05 mL, 0.68 mmol) in DCM (7.5 mL) at 0 °C for 1 h, to provide the title compound (0.33 g). LCMS (Method 11): 1.87 min, 594.1 $[M+H]^+$.

**Intermediate 306:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4,4'-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)hex-5-enamido)propanoate

**[00464]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 305** (0.27 g, 0.45 mmol), **Intermediate 258** (0.11 g, 0.45 mmol) and $K_2CO_3$ (63 mg, 0.45 mmol) in MeCN (6 mL) at 90 °C for 18 h. Purified by flash chromatography (24 g silica gel, eluting 0-3% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.11 g). (Method 15): 2.58 min, 732.2 $[M+H]^+$.

**Intermediate 307:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-6-en-13-yl)acetate

**[00465]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 306** (0.11 g, 0.10 mmol) in DCE (52 mL) and Grubbs II (8.8 mg, 0.01 mmol) at 40 °C for 24 h. Additional Grubbs II (4.4 mg, 5.0 µmol) were added and stirred at 40 °C for 24 h. Purified by flash

chromatography (12 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (67 mg). LCMS (Method 15): 2.51 min, 704.2 $[M+H]^+$.

**Intermediate 308:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00466]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 307** (67 mg, 0.06 mmol) and 10% palladium on carbon (6 mg) in ethanol (5.6 mL) under a hydrogen atmosphere at RT for 3 h, to provide the title compound (62 mg). LCMS (Method 15): 2.44 min, 706.5 $[M+H]^+$.

**Intermediate 309:** (2-(Benzyloxy)-4,6-dimethylphenyl)boronic acid

**[00467]** Prepared in an analogous manner to **Intermediate 121**, using magnesium (0.13 g, 5.15 mmol), iodomethane (8 µL, 0.12 mmol), 1-(benzyloxy)-2-bromo-3,5-dimethylbenzene (1.0 g, 3.43 mmol) in THF (6.9 mL) at 60 °C for 20 min, trimethyl borate (0.71 g, 6.87 mmol) in THF (6.9 mL) at -5 to 0 °C for 2 h. Run in two batches then combined crude was triturated in n-pentane to provide the title compound (1.49 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.42 – 7.36 (m, 5H), 6.72 (s, 1H), 6.67 (s, 1H), 5.78 (br s, 2H), 5.10 (s, 2H), 2.53 (s, 3H), 2.23 (s, 3H).

**Intermediate 310:** Ethyl (*S*)-3-amino-3-(5-bromo-2-fluoro-3-(trifluoromethyl)phenyl)propanoate

**[00468]** A suspension of ethyl (*S*)-3-(5-bromo-2-fluoro-3-(trifluoromethyl)phenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate (24.4 g, 52.7 mmol, CAS 2640364-18-5) in 4 M HCl in 1,4-dioxane (33 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure, dissolved in saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (15.0 g). LCMS (Method 22): 1.56 min, 359.9 $[M+H]^+$.

**Intermediate 311:** Ethyl (*S*)-3-amino-3-(3-bromo-5-cyclopropyl-2,6-difluorophenyl)propanoate

**[00469]** A suspension of ethyl (S)-3-(3-bromo-5-cyclopropyl-2,6-difluorophenyl)-3-(((R)-tert-butylsulfinyl)amino)propanoate (6.1 g, 13.5 mmol, CAS 2640469-83-4) in 4 M HCl in 1,4-dioxane (20 mL) and ethanol (15 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure, dissolved in water and basified with saturated aqueous $NaHCO_3$, then extracted with EtOAc. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (4.9 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.02 – 6.91 (m, 1H), 4.75 (dd, 1H), 4.18 – 4.08 (m, 2H), 2.97 – 2.86 (m, 1H), 2.74 (dd, 1H), 2.04 – 1.94 (m, 1H), 1.22 (t, 3H), 1.03 – 0.90 (m, 2H), 0.70 – 0.58 (m, 2H) – NHs not observed.

**Intermediate 312:** Ethyl (*S*)-3-(3-bromo-5-cyclopropyl-2,6-difluorophenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00470]** To a stirred suspension of **Intermediate 311** (4.94 g, 12.3 mmol) and Boc anhydride (3.23 g, 14.8 mmol) in DCM (40 mL) was added DIPEA (2.58 mL, 18.5 mmol) and the mixture stirred for 20 h at RT. The reaction mixture was diluted with DCM and washed with 1 M aqueous HCl, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (25 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (5.1 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 6.98 (t, 1H), 5.63 (s, 1H), 5.30 (s, 1H), 4.15 – 4.05 (m, 1H), 2.89 (dd, 1H), 2.80 (dd, 1H), 2.05 – 1.96 (m, 1H), 1.41 (s, 9H), 1.20 (t, 3H), 1.05 – 0.92 (m, 2H), 0.73 – 0.59 (m, 2H) – NH not observed.

**Intermediate 313:** Ethyl (3*S*)-3-(2'-(benzyloxy)-5-cyclopropyl-2,4-difluoro-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00471]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 309** (0.75 g, 2.94 mmol), **Intermediate 312** (1.20 g, 2.68 mmol), $K_3PO_4$ (1.71 g, 8.03 mmol) and XPhosPdG2 (0.21 g, 0.27 mmol) in 1,4-dioxane (60 mL), and water (6 mL) at 110 °C for 1.5 h. Purified by flash chromatography (40 g silica gel, eluting 0-25% EtOAc in petroleum ether) to provide the title compound (1.39 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.34 – 7.23 (m, 3H), 7.20 – 7.13 (m, 2H), 6.75 (s, 1H), 6.73 – 6.63 (m, 2H), 5.70 (s, 1H), 5.40 – 5.32 (m, 1H), 4.97 (s, 2H), 4.16 – 4.01 (m, 2H), 2.98 – 2.82 (m, 1H), 2.83 – 2.68 (m, 1H), 2.35 (s, 3H), 2.12 – 2.01 (m, 4H), 1.42 (s, 9H), 1.22 – 1.14 (m, 3H), 1.00 – 0.86 (m, 2H), 0.68 – 0.55 (m, 2H).

**Intermediate 314:** Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-2,4-difluoro-2'-hydroxy-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00472]** Prepared in an analogous manner to **Intermediate 127** using **Intermediate 313** (1.39 g, 2.39 mmol), ammonium formate (3.77 g, 59.8 mmol), 10% palladium on carbon (0.51 g, 0.48 mmol) in ethanol (25 mL) at reflux for 24 h. Additional ammonium formate (0.96 g, 19.1 mmol) and 10% palladium on carbon (0.12 g, 0.12 mmol) was added and heating continued for 1.5 h. Additional 10% palladium on carbon (0.28 g, 0.26 mmol) was added and heating continued for 24 h, to provide the title compound (1.08 g). LCMS (Method 22): 1.80 min, 390.1 $[M\text{-Boc}+H]^+$.

**Intermediate 315:** Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-2,4-difluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00473]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 314** (1.08 g, 2.20 mmol), $K_2CO_3$ (1.07 g, 7.71 mmol) and 5-bromopent-1-ene (0.65 mL, 5.51 mmol) in

MeCN (16 mL) at reflux for 16 h to provide the title compound (1.21 g). LCMS (Method 7): 2.72 min, 458.1 $[M-Boc+H]^+$.

**Intermediate 316:** Ethyl (3*S*)-3-amino-3-(5-cyclopropyl-2,4-difluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00474]** A suspension of **Intermediate 315** (1.21 g, 2.17 mmol) in 4 M HCl in 1,4-dioxane (5 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (1.07 g). LCMS (Method 22): 1.99 min, 458.1 $[M+H]^+$.

**Intermediate 317:** Ethyl (3*S*)-3-(5-cyclopropyl-2,4-difluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00475]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 316** (1.07 g, 2.17 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.28 g, 2.39 mmol, CAS 413622-10-3), DIPEA (0.97 mL, 5.43 mmol), HOBt (0.35 g, 2.60 mmol) and EDCI (0.50 g, 2.60 mmol) in MeCN (14.5 mL) at RT for 16 h, to provide the title compound (0.64 g). LCMS (Method 22): 1.95 min, 556.2 $[M+H]^+$.

**Intermediate 318:** Ethyl (3*S*)-3-(5-cyclopropyl-2,4-difluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00476]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 317** (0.96 g, 1.74 mmol), triethylamine (0.48 mL, 3.47 mmol) and methanesulfonyl chloride (0.20 mL, 2.60 mmol) in DCM (8 mL) at 0 °C for 2 h, to provide the title compound (1.01 g). LCMS (Method 22): 2.00 min, 634.2 $[M+H]^+$.

**Intermediate 319:** Ethyl (3*S*)-3-(5-cyclopropyl-2,4-difluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00477]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 318** (0.55 g, 0.86 mmol), **Intermediate 258** (0.25 g, 1.13 mmol) and $K_2CO_3$ (0.36 g, 2.60 mmol) in MeCN (4 mL) at reflux for 18 h. Purified by flash chromatography (25 g silica gel, eluting 25% (1:1 EtOAc / ethanol) in petroleum ether) to provide the title compound (0.10 g). LCMS (Method 12): 2.15 min, 772.6 $[M+H]^+$.

**Intermediate 320:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^2$,$1^4$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00478]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 319** (0.10 g, 0.13 mmol) in DCE (10 mL) and Grubbs II (11 mg, 13 μmol) at 50 °C for 24 h. Purified by

flash chromatography (20 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (59 mg). LCMS (Method 15): 2.58 min, 742.7 $[M-H]^-$.

**Intermediate 321:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^2$,$1^4$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00479]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 320** (40 mg, 0.05 mmol) and 10% palladium on carbon (5.7 mg) in ethanol (4 mL) under a hydrogen atmosphere at RT for 4 h, to provide the title compound (40 mg). LCMS (Method 11): 2.64 min, 746.4 $[M+H]^+$.

**Intermediate 322:** 2-(6-Methoxy-4-(trifluoromethyl)pyridin-3-yl)acetaldehyde

**[00480]** A solution of **Intermediate 255** (2.05 g, 8.28 mmol) in TFA (10.2 mL) was stirred at RT for 6 h. The mixture was concentrated under reduced pressure to provide the title compound (2.08 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 9.78 (s, 1H), 8.45 (s, 1H), 7.35 (s, 1H), 4.17 (s, 3H), 4.05 (s, 2H).

**Intermediate 323:** 2-Methoxy-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridine

**[00481]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 322** (2.08 g, 8.06 mmol), pyrrolidine (0.79 mL, 9.67 mmol), triethylamine (1.35 mL, 9.67 mmol) in DCM (28 mL) and 4 Å molecular sieves at RT for 2 h, then STAB (3.42 g, 16.1 mmol) at RT for 16 h. Purified by dry flash chromatography (silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (1.54 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 8.18 (s, 1H), 6.92 (s, 1H), 3.90 (s, 3H), 3.05 – 2.99 (m, 2H), 2.97 – 2.82 (m, 6H), 1.98 –1.87 (m, 4H).

**Intermediate 324:** 5-(2-(Pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-2(1*H*)-one

**[00482]** A solution of **Intermediate 323** (0.75 g, 2.75 mmol) in 33% HBr in AcOH (4.74 mL, 27.5 mmol) was stirred at 85 °C for 3 h. The mixture was cooled and concentrated under reduced pressure. The crude product was purified by catch and release chromatography (20 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.55 g). $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.56 (s, 1H), 6.81 (s, 1H), 2.80 – 2.73 (m, 2H), 2.72 – 2.62 (m, 6H), 1.89 – 1.81 (m, 4H).

**Intermediate 325:** Ethyl (*S*)-3-(4-fluoro-2',4',5-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00483]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 287** (0.42 g, 0.69 mmol), **Intermediate 324** (0.18 g, 0.69 mmol) and $K_2CO_3$ (0.29 g, 2.07 mmol) in MeCN

(8.3 mL) at 90 °C for 16 h. Purified by reverse phase chromatography (55 g C18, eluting 20-60% MeCN in 0.1% aqueous formic acid) to provide the title compound (90 mg). LCMS (Method 18): 1.51 min, 754.3 $[M+H]^+$.

**Intermediate 326:** Ethyl 2-((10*S*,13*S*)-1$^4$-fluoro-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00484]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 325** (0.12 g, 0.16 mmol) in DCE (74 mL) and Grubbs II (13 mg, 16 µmol) at 40 °C for 48 h. Purified by flash chromatography (25 g silica gel, eluting 0-8% (0.5% ammonia MeOH) in DCM) to provide the title compound (83 mg). LCMS (Method 7): 1.90 min, 726.3 $[M+H]^+$.

**Intermediate 327:** Ethyl 2-((10*S*,13*S*)-1$^4$-fluoro-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00485]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 326** (83 mg, 0.12 mmol) and 10% palladium on carbon (12 mg) in ethanol (13 mL) under a hydrogen atmosphere at RT for 2 h, to provide the title compound (71 mg). LCMS (Method 21): 5.79 min, 728.3 $[M+H]^+$.

**Intermediate 328:** Ethyl (*S*)-3-(4,4'-difluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00486]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 239** (0.47 g, 0.68 mmol), **Intermediate 324** (0.18 g, 0.68 mmol) and $K_2CO_3$ (0.28 g, 2.04 mmol) in MeCN (2.5 mL) at 90 °C for 16 h. Purified by reverse phase chromatography (55 g C18, eluting 20-60% MeCN in 0.1% aqueous formic acid) to provide the title compound (0.13 g). LCMS (Method 7): 1.98 min, 758.3 $[M+H]^+$.

**Intermediate 329:** Ethyl 2-((10*S*,13*S*)-1$^4$,2$^4$-difluoro-1$^5$,2$^6$-dimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00487]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 328** (0.17 g, 0.22 mmol) in DCE (74 mL) and Grubbs II (19 mg, 22 µmol) at 40 °C for 24 h. Purified by flash chromatography (40 g silica gel, eluting 0-8% (0.5% ammonia MeOH) in DCM) to provide the title compound (83 mg). LCMS (Method 15): 2.64 min, 730.3 $[M+H]^+$.

**Intermediate 330:** Ethyl 2-((10*S*,13*S*)-1$^4$,2$^4$-difluoro-1$^5$,2$^6$-dimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00488]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 329** (0.12 g, 0.16 mmol) and 10% palladium on carbon (17 mg) in ethanol (13 mL) under a hydrogen atmosphere at RT for 2 h, to provide the title compound (0.10 g). LCMS (Method 15): 2.70 min, 732.3 $[M+H]^+$.

**Intermediate 331:** 2-(6-Methoxy-4-methylpyridin-3-yl)-*N*,*N*-dimethylethan-1-amine

**[00489]** Prepared in an analogous manner to **Intermediate 137** using 2-(6-methoxy-4-methylpyridin-3-yl)acetaldehyde (3.60 g, 21.8 mmol, CAS 2378704-97-1), dimethylamine (1.74 mL, 26.2 mmol), triethylamine (3.65 mL, 26.2 mmol) in DCM (44 mL) and 4 Å molecular sieves at RT for 1.5 h, then STAB (9.25 g, 43.6 mmol) at RT for 16 h. Purified by flash chromatography (12 g silica gel, eluting 0-6% MeOH in DCM) then by dry flash chromatography (silica gel, 0–10% (0.1% ammonia MeOH) in DCM) followed by reverse phase chromatography (55 g C18, 10-60% MeCN in 0.1% aqueous ammonia) to provide the title compound (1.39 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.85 (s, 1H), 6.50 (s, 1H), 3.84 (s, 3H), 2.73 – 2.69 (m, 2H), 2.50 – 2.46 (m, 2H), 2.35 (s, 6H), 2.23 (d, 3H).

**Intermediate 332:** 5-(2-(Dimethylamino)ethyl)-4-methylpyridin-2(1*H*)-one

**[00490]** A solution of **Intermediate 331** (1.39 g, 7.17 mmol) in 33% HBr in AcOH (12.4 mL, 71.7 mmol) was stirred at 85 °C for 6 h. The mixture was cooled and concentrated under reduced pressure. The crude product was purified by catch and release chromatography (20 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.87 g). $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.24 (s, 1H), 6.39 (s, 1H), 2.63 – 2.59 (m, 2H), 2.47 – 2.43 (m, 2H), 2.31 (s, 6H), 2.25 (s, 3H).

**Intermediate 333:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(4-fluoro-2',4',5-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00491]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 287** (0.51 g, 0.74 mmol), **Intermediate 332** (0.15 g, 0.81 mmol) and $K_2CO_3$ (0.31 g, 2.22 mmol) in MeCN (9.2 mL) at 90 °C for 16 h. Purified by flash chromatography (40 g silica gel, eluting 3-8% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.14 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.70 (br s, 1H), 7.26 (d, 1H), 6.96 – 6.92 (m, 2H), 6.67 (s, 1H), 6.57 (d, 1H), 6.35 (d, 1H), 5.74 – 5.66 (m, 1H), 5.61 – 5.49 (m, 3H), 5.02 – 4.97 (m, 1H), 4.94 – 4.91 (m, 3H), 3.96

– 3.91 (m, 2H), 3.82 (t, 2H), 2.80 – 2.74 (m, 3H), 2.60 – 2.36 (m, 5H), 2.31 (s, 3H), 2.30 (d, 6H), 2.25 (s, 3H), 2.14 (s, 3H), 2.01 – 1.95 (m, 5H), 1.67 – 1.61 (m, 2H), 1.08 (t, 3H).

**Intermediate 334:** Ethyl 2-((10*S*,13S)-10-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00492]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 333** (0.16 g, 0.24 mmol) in DCE (0.11 L) and Grubbs II (20 mg, 24 µmol) at 40 °C for 24 h. Purified by flash chromatography (25 g silica gel, eluting 0-8% (0.5% ammonia MeOH) in DCM) to provide the title compound (62 mg). LCMS (Method 7): 1.74 min, 646.3 $[M+H]^+$.

**Intermediate 335:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00493]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 334** (62 mg, 0.10 mmol) and 10% palladium on carbon (10 mg) in ethanol (11 mL) under a hydrogen atmosphere at RT for 2 h. Purified by reverse phase chromatography (20 g C18, 30-60% MeCN in 0.1% aqueous formic acid) to provide the title compound (44 mg). LCMS (Method 21): 5.01 min, 648.3 $[M+H]^+$.

**Intermediate 336:** 5-Bromo-2-iodo-3-methylphenol

**[00494]** To a solution of 2-amino-5-bromo-3-methylphenol (3.06 g, 12.4 mmol, CAS 1194760-84-3) in THF (80 mL) and MeCN (80 mL) at -40 °C was added $BF_3.OEt_2$ (4.44 mL, 37.3 mmol) and stirred at -40 °C for 10 min. To this was added t-butyl nitrite (2.46 mL, 18.6 mmol) and the mixture was stirred at -40 °C for 1 h. Petroleum ether was added to form a precipitate, then the supernatant was decanted off and the residue taken up in MeCN (80 mL). To this solution was added potassium iodide (3.05 g, 0.12 mol) and iodine (11.7 g, 46.0 mmol) and was stirred at 55 °C for 18 h. The reaction was quenched with saturated aqueous sodium thiosulfate and extracted with EtOAc. The combined organics were washed with brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica, 0–25% EtOAc in petroleum ether) to provide the title compound (3.30 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.00 – 6.98 (m, 2H), 5.48 (s, 1H), 2.42 (s, 3H).

**Intermediate 337:** Ethyl (*S*)-3-(4'-bromo-4-fluoro-2'-hydroxy-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00495]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 234** (1.50 g, 3.23 mmol), **Intermediate 336** (1.14 g, 3.66 mmol), $Na_2CO_3$ (1.06 g, 9.97 mmol) and $Pd(dppf)Cl_2$ (0.27 g, 0.33 mmol) in 1,4-dioxane (30 mL), and water (3 mL) at 85 °C for 18 h.

Purified by flash chromatography (40 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.76 g). LCMS (Method 11): 2.29 min, 510.5 $[M-H]^-$.

**Intermediate 338:** Ethyl (*S*)-3-((*tert*-Butoxycarbonyl)amino)-3-(4'-cyclopropyl-4-fluoro-2'-hydroxy-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00496]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 337** (1.06 g, 1.96 mmol), cyclopropaneboronic acid (0.67 g, 7.84 mmol), $K_3PO_4$ (1.25 g, 5.88 mmol), palladium acetate (44 mg, 0.20 mmol) and tricyclohexyl phosphine (55 mg, 0.20 mmol) in toluene (20 mL) and water (4 mL) at 120 °C for 18 h. Additional cyclopropaneboronic acid (0.34 g, 3.92 mmol), palladium acetate (22 mg, 0.10 mmol) and tricyclohexyl phosphine (27 mg, 0.10 mmol) were added and stirred at 120 °C for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-25% EtOAc in petroleum ether) to provide the title compound (0.79 g). LCMS (Method 15): 2.31 min, 494.1 $[M+Na]^+$.

**Intermediate 339:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4'-cyclopropyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00497]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 338** (0.86 g, 1.00 mmol), $K_2CO_3$ (0.48 g, 3.46 mmol) and 4-bromobut-1-ene (0.21 mL, 2.08 mmol) in MeCN (17 mL) at reflux for 24 h. Additional $K_2CO_3$ (0.47 g, 3.46 mmol) and 4-bromobut-1-ene (0.39 mL, 3.80 mmol) were added and refluxed for 24 h. Additional $K_2CO_3$ (0.72 g, 5.19 mmol) and 4-bromobut-1-ene (0.26 mL, 2.59 mmol) were added and refluxed for 24 h. Purified by flash chromatography (40 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.58 g). LCMS (Method 7): 2.76 min, 426.2 $[M-Boc+H]^+$.

**Intermediate 340:** Ethyl (*S*)-3-amino-3-(2'-(but-3-en-1-yloxy)-4'-cyclopropyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00498]** A suspension of **Intermediate 339** (0.56 g, 1.07 mmol) in 4 M HCl in 1,4-dioxane (5 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure to provide the title compound (0.65 g). LCMS (Method 12): 1.92 min, 426.4 $[M+H]^+$.

**Intermediate 341:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4'-cyclopropyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxyhex-5-enamido)propanoate

**[00499]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 340** (0.65 g, 1.06 mmol), (2*R*)-2-hydroxyhex-5-enoic acid (0.21 g, 1.58 mmol, CAS 612825-60-2), DIPEA (0.60 mL, 4.22 mmol), HOBt (0.16 g, 1.61 mmol) and EDCI (0.30 g, 1.58 mmol) in MeCN (10 mL) at RT for 16 h. Purified by flash chromatography (12 g silica gel, eluting 10-60% EtOAc in petroleum ether) to provide the title compound (0.19 g). LCMS (Method 12): 1.92 min, 538.4 $[M+H]^+$.

**Intermediate 342:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4'-cyclopropyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)hex-5-enamido)propanoate

**[00500]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 341** (0.19 g, 0.30 mmol), triethylamine (0.08 mL, 0.60 mmol) and methanesulfonyl chloride (0.04 mL, 0.45 mmol) in DCM (3 mL) at 0 °C for 5 min, to provide the title compound (0.20 g). LCMS (Method 22): 1.93 min, 616.2 $[M+H]^+$.

**Intermediate 343:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4'-cyclopropyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)hex-5-enamido)propanoate

**[00501]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 342** (0.20 g, 0.31 mmol), **Intermediate 258** (94 mg, 0.40 mmol) and $K_2CO_3$ (0.13 g, 0.93 mmol) in MeCN (3 mL) at reflux for 18 h. Purified by flash chromatography (24 g silica gel, eluting 6% MeOH in DCM) to provide the title compound (67 mg). LCMS (Method 25): 3.49 min, 754.3 $[M+H]^+$.

**Intermediate 344:** Ethyl 2-((10*S*,13*S*)-2$^4$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-6-en-13-yl)acetate

**[00502]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 343** (67 mg, 0.09 mmol) in DCE (25 mL) and Grubbs II (7.5 mg, 9 µmol) at 50 °C for 18 h. Additional Grubbs II (7.5 mg, 9 µmol) was added and heating continued at 50 °C for 88 h. Purified by flash chromatography (12 g silica gel, eluting 0-5% MeOH in DCM) to provide the title compound (32 mg). LCMS (Method 12): 2.01 min, 724.8 $[M-H]^-$.

**Intermediate 345:** Ethyl 2-((10*S*,13*S*)-2$^4$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00503]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 344** (32 mg, 4.4 µmol) and 10% palladium on carbon (5 mg) in ethanol (3.5 mL) under a hydrogen atmosphere at RT for 4 h, to provide the title compound (33 mg). LCMS (Method 22): 2.02 min, 728.3 $[M+H]^+$.

**Intermediate 346:** Ethyl (*S*)-3-(5-bromo-2-fluoro-3-(trifluoromethyl)phenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00504]** To a stirred suspension of **Intermediate 310** (14.1 g, 35.4 mmol) and Boc anhydride (9.28 g, 42.5 mmol) in DCM (0.18 L) was added DIPEA (9.26 mL, 53.2 mmol) and the mixture stirred at RT for 72 h. The reaction mixture was diluted with DCM and washed with 1 M

aqueous HCl, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was triturated in petroleum ether and filtered to provide the title compound (12.7 g). LCMS (Method 22): 1.86 min, 357.9 $[M\text{-}Boc+H]^+$.

**Intermediate 347:** Ethyl (*S*)-3-(2'-(benzyloxy)-4-fluoro-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00505]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 309** (0.41 g, 1.08 mmol), **Intermediate 346** (0.42 g, 1.62 mmol), $K_3PO_4$ (0.69 g, 3.24 mmol) and XPhosPdG2 (85 mg, 0.11 mmol) in 1,4-dioxane (37 mL), and water (6 mL) at 110 °C for 1.5 h. Purified by flash chromatography (25 g silica gel, eluting 10-100% EtOAc in petroleum ether) to provide the title compound (1.39 g). $^1H$ NMR (400 MHz; $CDCl_3$) δ: 7.49 (s, 2H), 7.32 – 7.20 (m, 3H), 7.20 – 7.14 (m, 2H), 6.75 (d, 2H), 5.86 (d, 1H), 5.46 (s, 1H), 4.98 (s, 2H), 4.07 – 3.87 (m, 2H), 2.96 – 2.71 (m, 2H), 2.36 (s, 3H), 2.08 (s, 3H), 1.30 (s, 9H), 1.12 (t, 3H).

**Intermediate 348:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2'-hydroxy-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00506]** Prepared in an analogous manner to **Intermediate 127** using **Intermediate 347** (1.02 g, 1.73 mmol), ammonium formate (2.18 g, 34.6 mmol), 10% palladium on carbon (0.18 g, 0.17 mmol) in ethanol (17 mL) at 80 °C for 24 h. Additional ammonium formate (2.18 g, 34.6 mmol) and 10% palladium on carbon (0.18 g, 0.17 mmol) was added and heating continued for 5 h, to provide the title compound (0.85 g). LCMS (Method 7): 2.20 min, 400.9 $[M\text{-}Boc+H]^+$.

**Intermediate 349:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00507]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 348** (0.93 g, 1.85 mmol), $K_2CO_3$ (0.38 g, 2.78 mmol) and 5-bromopent-1-ene (0.24 mL, 2.04 mmol) in MeCN (21 mL) at reflux for 16 h to provide the title compound (0.77 g). LCMS (Method 18): 2.10 min, 468.1 $[M\text{-}Boc+H]^+$.

**Intermediate 350:** Ethyl (*S*)-3-(4-fluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00508]** A suspension of **Intermediate 349** (0.77 g, 1.36 mmol) in 4 M HCl in 1,4-dioxane (6.8 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure. This was suspended in MeCN (12 mL) and (2*R*)-2-hydroxypent-4-enoic acid (0.23 g, 2.00 mmol, CAS 413622-10-3), DIPEA (0.93 mL, 5.32 mmol), HOBt (0.20 g, 1.46 mmol) and EDCI (0.38 g, 2.00 mmol) and the mixture was stirred at RT for 16 h. The mixture was diluted with water and extracted into EtOAc. The organic layer was washed with saturated $NaHCO_3$, 1 M aqueous HCl, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure.

The crude product was purified by flash chromatography (25 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.68 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.86 (d, 1H), 7.43 – 7.37 (m, 2H), 6.69 (s, 1H), 6.60 (s, 1H), 5.72 – 5.61 (m, 3H), 5.03 (d, 1H), 4.96 – 4.87 (m, 3H), 4.18 – 4.14 (m, 1H), 4.07 – 4.01 (m, 2H), 3.84 (t, 2H), 2.95 – 2.85 (m, 2H), 2.55 – 2.50 (m, 1H), 2.41 – 2.28 (m, 5H), 2.01 (d, 3H), 1.95 (q, 2H), 1.68 – 1.62 (m, 2H), 1.14 (t, 3H).

**Intermediate 351:** Ethyl (*S*)-3-(4-fluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00509]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 350** (0.45 g, 0.79 mmol), triethylamine (0.22 mL, 1.59 mmol) and methanesulfonyl chloride (0.09 mL, 1.19 mmol) in DCM (5 mL) at 0 °C for 1 h, to provide the title compound (0.47 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.72 (s, 1H), 7.45 – 7.36 (m, 2H), 6.72 (s, 1H), 6.61 (s, 1H), 5.75 – 5.65 (m, 3H), 5.11 – 5.04 (m, 2H), 5.00 – 4.89 (m, 3H), 4.12 – 4.04 (m, 2H), 3.85 (t, 2H), 3.11 (d, 3H), 2.99 – 2.89 (m, 2H), 2.70 – 2.57 (m, 2H), 2.35 (s, 3H), 2.04 – 1.94 (m, 5H), 1.66 (q, 2H), 1.17 (t, 3H).

**Intermediate 352:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4-fluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00510]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 351** (0.47 g, 0.68 mmol), **Intermediate 258** (0.16 g, 0.68 mmol) and $K_2CO_3$ (0.28 g, 2.03 mmol) in MeCN (9.5 mL) at reflux for 18 h. Purified by reverse phase chromatography (38 g C18, eluting 20-50% MeCN in 0.1% aqueous formic acid) to provide the title compound (92 mg). LCMS (Method 7): 1.99 min, 782.3 $[M+H]^+$.

**Intermediate 353:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00511]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 352** (92 mg, 0.12 mmol) in DCE (58 mL) and Grubbs II (10 mg, 12 μmol) at 40 °C for 48 h. Purified by flash chromatography (25 g silica gel, eluting 0-8% (0.5% ammonia MeOH) in DCM) to provide the title compound (85 mg). LCMS (Method 15): 2.62 min, 754.2 $[M+H]^+$.

**Intermediate 354:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00512]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 353** (85 mg, 0.09 mmol) and 10% palladium on carbon (9.4 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 2 h, to provide the title compound (78 mg). LCMS (Method 15): 2.73 min, 756.3 $[M+H]^+$.

**Intermediate 355:** Methyl (*S*)-3-(2'-(allyloxy)-4'-fluoro-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00513]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 80** (0.50 g, 1.24 mmol), $K_2CO_3$ (0.19 g, 1.37 mmol) and allyl bromide (0.12 mL, 1.38 mmol) in MeCN (10 mL) at reflux for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.47 g). LCMS (Method 22): 1.83 min, 344.0 $[M-Boc+H]^+$.

**Intermediate 356:** Methyl (*S*)-3-(2'-(allyloxy)-4'-fluoro-6'-methyl-[1,1'-biphenyl]-3-yl)-3-aminopropanoate hydrochloride

**[00514]** A suspension of **Intermediate 355** (0.47 g, 1.36 mmol) in 4 M HCl in 1,4-dioxane (0.96 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (0.48 g). LCMS (Method 22): 1.55 min, 344.0 $[M+H]^+$.

**Intermediate 357:** Methyl (*S*)-3-(2'-(allyloxy)-4'-fluoro-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((R)-2-hydroxypent-4-enamido)propanoate

**[00515]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 356** (0.37 g, 0.99 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.17 g, 1.48 mmol, CAS 413622-10-3), DIPEA (0.67 mL, 3.95 mmol), HOBt (0.15 g, 1.09 mmol) and EDCI (0.28 g, 1.48 mmol) in MeCN (6.5 mL) at RT for 16 h, to provide the title compound (0.32 g). LCMS (Method 22): 1.57 min, 442.1 $[M+H]^+$.

**Intermediate 358:** Methyl (*S*)-3-(2'-(allyloxy)-4'-fluoro-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00516]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 357** (0.32 g, 0.67 mmol), triethylamine (0.19 mL, 1.34 mmol) and methanesulfonyl chloride (0.12 mL, 1.48 mmol) in DCM (10 mL) at 0 °C for 10 min then RT for 1 h, to provide the title compound (0.47 g). LCMS (Method 15): 2.09 min, 520.1 $[M+H]^+$.

**Intermediate 359:** Methyl (*S*)-3-(2'-(allyloxy)-4'-fluoro-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00517]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 137** (0.13 g, 0.81 mmol), **Intermediate 358** (0.35 g, 0.67 mmol) and $K_2CO_3$ (0.28 g, 2.02 mmol) in MeCN

(5 mL) at 85 °C for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.16 g). LCMS (Method 15): 2.06 min, 590.3 $[M+H]^+$.

**Intermediate 360:** Methyl 2-((8*S*,11*S*)-8-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$2^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphan-5-en-11-yl)acetate

**[00518]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 359** (85 mg, 0.14 mmol) in DCE (44 mL) and Hoveyda-Grubbs M720 (4.5 mg, 7 µmol) at 40 °C for 20 h. Additional Hoveyda-Grubbs M720 (9 mg, 14 µmol) added and heated at 40 °C for 96 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (23 mg). LCMS (Method 11): 1.95 min, 560.6 $[M-H]^-$.

**Intermediate 361:** Methyl 2-((8*S*,11*S*)-8-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$2^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetate

**[00519]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 360** (23 mg, 0.04 mmol) and 10% palladium on carbon (4.4 mg) in ethanol (4 mL) under a hydrogen atmosphere at RT for 2 h, to provide the title compound (24 mg). LCMS (Method 19): 3.97 min, 562.6 $[M-H]^-$.

**Intermediate 362:** Ethyl (3*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-2,4-difluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00520]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 318** (1.74 g, 2.75 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.66 g, 2.75 mmol, CAS 109919-32-6) and $K_2CO_3$ (1.14 g, 8.24 mmol) in MeCN (20 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.95 g). LCMS (Method 22): 2.18 min, 781.2 $[M+H]^+$.

**Intermediate 363:** Ethyl 2-((10*S*,13*S*)-10-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$-cyclopropyl-$1^2$,$1^4$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00521]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 362** (0.95 g, 0.99 mmol) in DCE (0.30 L) and Grubbs II (84 mg, 0.10 mmol) at 40 °C for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (85 mg). LCMS (Method 22): 2.72 min, 751.2 $[M+H]^+$.

**Intermediate 364:** Ethyl 2-((10*S*,13*S*)-1$^5$-cyclopropyl-10-(5-((*E*)-2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^2$,1$^4$-difluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00522]** A mixture of **Intermediate 363** (0.34 g, 0.44 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (88 mg, 0.44 mmol, CAS 1201905-61-4) and $Na_2CO_3$ (0.80 g, 7.56 mmol) in 1,4-dioxane (14.5 mL) and water (5 mL) was degassed with nitrogen. To this was added Pd(dppf)$Cl_2$ (33 mg, 0.04 mmol) and the reaction mixture stirred at 90 °C for 18 h. The mixture was diluted with water and extracted into EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure, to provide the title compound (0.55 g). LCMS (Method 22): 2.11 min, 743.2 $[M+H]^+$.

**Intermediate 365:** 2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-((*E*)-2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^2$,1$^4$-difluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetic acid

**[00523]** A solution of **Intermediate 364** (0.55 g, 0.74 mmol) and lithium hydroxide (53 mg, 2.21 mmol) in THF (16 mL), MeOH (10 mL) and water (10 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure and the crude was purified by reverse phase chromatography (38 g C18, eluting 30-70% MeCN in 0.1% aqueous ammonia) to provide the title compound (0.15 g). LCMS (Method 22): 1.28 min, 715.2 $[M+H]^+$.

**Intermediate 366:** 2-((10*S*,13*S*)-1$^5$-Cyclopropyl-1$^2$,1$^4$-difluoro-2$^4$,2$^6$-dimethyl-11-oxo-10-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetic acid

**[00524]** A solution of **Intermediate 365** (0.15 g, 0.21 mmol) in DCM (5 mL) and TFA (1.02 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.14 g). LCMS (Method 22): 1.24 min, 687.1 $[M+H]^+$.

**Intermediate 367:** 2-((10*S*,13*S*)-10-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^5$-cyclopropyl-1$^2$,1$^4$-difluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetic acid

**[00525]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 366** (0.14 g, 0.21 mmol), azetidine (17 µL, 0.25 mmol), triethylamine (0.23 mL, 1.66 mmol) in DCM (1.3 mL) and 4 Å molecular sieves at RT for 4.5 h, then STAB (88 mg, 0.41 mmol) at RT for 18 h, to provide the title compound (0.57 g). LCMS (Method 22): 1.38 min, 728.2 $[M+H]^+$.

**Intermediate 368:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4-fluoro-2',4',5-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00526]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 287** (0.62 g, 1.06 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.26 g, 1.06 mmol, CAS 109919-32-6) and $K_2CO_3$ (0.44 g, 3.17 mmol) in MeCN (10 mL) at 80 °C for 20 h. Purified by flash chromatography (20 g silica gel, eluting 0-45% EtOAc in petroleum ether) to provide the title compound (0.20 g). LCMS (Method 12): 2.14 min, 737.4 $[M+H]^+$.

**Intermediate 369:** Ethyl 2-((10*S*,13*S*)-10-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00527]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 368** (0.20 g, 0.99 mmol) in DCE (15 mL) and Grubbs II (21 mg, 0.03 mmol) at 50 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-15% EtOAc in petroleum ether) to provide the title compound (0.15 g). LCMS (Method 19): 5.61 min, 709.4 $[M+H]^+$.

**Intermediate 370:** Ethyl 2-((10*S*,13*S*)-10-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00528]** A mixture of **Intermediate 369** (0.10 g, 0.14 mmol), $Pd(PPh_3)_2Cl_2$ (10 mg, 14 µmol) and copper(I) iodide (3 mg, 16 µmol) in MeCN (2 mL) was degassed with nitrogen. Triethylamine (0.10 mL, 0.72 mmol) and *N*,*N*-dimethylpropargylamine (0.10 mL, 0.93 mmol, CAS 7223-38-3) were added and the reaction mixture stirred at 60 °C for 20 h. The mixture was filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (12 g silica gel, eluting 0-100% EtOAc in petroleum ether), to provide the title compound (61 mg). LCMS (Method 19): 5.37 min, 710.7 $[M+H]^+$.

**Intermediate 371:** Ethyl 2-((10*S*,13*S*)-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00529]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 370** (61 mg, 0.08 mmol) and 10% palladium on carbon (8 mg) in ethanol (8 mL) under a hydrogen atmosphere at RT for 2 h. Additional 10% palladium on carbon (8 mg) was added and stirred under a hydrogen atmosphere at RT for 3 h. Purified by catch and release chromatography (1 g SCX, eluting MeOH followed by 7 M ammonia in MeOH) to provide the title compound (23 mg). LCMS (Method 19): 5.83 min, 716.2 $[M+H]^+$.

**Intermediate 372:** (*R*,*E*)-*N*-(3-bromo-5-chloro-2-fluorobenzylidene)-2-methylpropane-2-sulfinamide

**[00530]** Prepared in an analogous manner to **Intermediate 102** using 3-bromo-5-chloro-2-fluorobenzaldehyde (4.00 g, 16.8 mmol, CAS 1269440-82-5), (*R*)-2-methylpropane-2-sulfinimide (2.25 g, 18.5 mmol, CAS 196929-78-9) and titanium ethoxide (5.76 g, 25.3 mmol) in THF (40 mL) at 40 °C for 19 h, to provide the title compound (6.15 g). LCMS (Method 22): 1.78 min, 341.8 $[M+H]^+$.

**Intermediate 373:** Ethyl (*S*)-3-(3-bromo-5-chloro-2-fluorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

**[00531]** Prepared in an analogous manner to **Intermediate 104** using zinc (5.9 g, 90.3 mmol) chlorotrimethylsilane (0.46 mL, 3.61 mmol) and ethyl bromoacetate (5.0 mL, 45.1 mmol) in THF (0.12 L) at 60 °C for 1 h, then **Intermediate 372** (6.15 g, 18.1 mmol) in THF (25 mL) at RT for 18 h. Purified by flash chromatography (80 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (4.04 g). LCMS (Method 22): 1.69 min, 430.2 $[M+H]^+$.

**Intermediate 374:** Ethyl (*S*)-3-amino-3-(3-bromo-5-chloro-2-fluorophenyl)propanoate

**[00532]** A suspension of **Intermediate 373** (4.04 g, 9.42 mmol) in 4 M HCl in 1,4-dioxane (15 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure then purified by catch and release chromatography (20 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (2.49 g). LCMS (Method 12): 1.65 min, 323.9 $[M+H]^+$.

**Intermediate 375:** Ethyl (*S*)-3-(3-bromo-5-chloro-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00533]** To a stirred suspension of **Intermediate 374** (2.49 g, 7.66 mmol) and Boc anhydride (2.01 g, 9.20 mmol) in DCM (20 mL) was added DIPEA (2.00 mL, 11.5 mmol) and the mixture stirred for 5 h at RT. The reaction mixture was washed with 1 M aqueous HCl, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (1.13 g). LCMS (Method 22): 1.76 min, 323.9 $[M-Boc+H]^+$.

**Intermediate 376:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-chloro-3-cyclopropyl-2-fluorophenyl)propanoate

**[00534]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 375** (1.00 g, 2.36 mmol), cyclopropaneboronic acid (0.25 g, 2.94 mmol), $K_2CO_3$ (0.98 g, 7.06 mmol), $Pd(dtbpf)Cl_2$ (77 mg, 0.12 mmol) in toluene (25 mL) at 70 °C for 3 h. Conditions were repeated with cyclopropaneboronic acid (51 mg, 0.59 mmol), $K_2CO_3$ (0.20 g, 1.41 mmol), $Pd(dtbpf)Cl_2$ (15 mg, 0.02 mmol) in toluene (25 mL) at 70 °C for 3 h. Purified by flash chromatography (12

g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.73 g). LCMS (Method 26): 2.31 min, 286.2 $[M\text{-}Boc+H]^+$.

**Intermediate 377:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(3-cyclopropyl-2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate

**[00535]** Prepared in an analogous manner to **Intermediate 2** using **Intermediate 376** (0.49 g, 1.12 mmol), bis(pinacolato)diboron (0.57 g, 2.24 mmol), potassium acetate (25 mg, 0.11 mmol) and SPhos (46 mg, 0.11 mmol) in DME (19 mL) at 105 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.38 g). LCMS (Method 12): 1.94 min, 378.3 $[M\text{-}Boc+H]^+$.

**Intermediate 378:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-2'-hydroxy-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00536]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 377** (0.38 g, 0.80 mmol), 2-bromo-3,5-dimethylphenol (0.24 g, 1.20 mmol), $K_3PO_4$ (0.34 g, 1.61 mmol), palladium acetate (18 mg, 0.08 mmol) and tricyclohexyl phosphine (23 mg, 0.08 mmol) in toluene (7.1 mL) and water (0.9 mL) at 100 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.27 g). $^1H$ NMR (400 MHz; $CDCl_3$) δ: 7.02 (d, 1H), 6.68 – 6.66 (m, 3H), 5.72 (s, 1H), 5.36 (s, 1H), 4.09 – 4.04 (m, 2H), 2.87 (d, 2H), 2.30 (s, 3H), 2.15 – 2.11 (m, 1H), 1.98 (s, 3H), 1.41 (s, 9H), 1.20 – 1.17 (m, 3H), 1.01 (d, 2H), 0.69 (s, 2H) – NH not observed.

**Intermediate 379:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00537]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 378** (0.59 g, 1.13 mmol), $K_2CO_3$ (0.23 g, 1.69 mmol) and 5-bromopent-1-ene (0.15 mL, 1.24 mmol) in MeCN (19 mL) at reflux for 16 h. Additional 5-bromopent-1-ene (0.15 mL, 1.24 mmol) was added and heated at reflux for 24 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.22 g). LCMS (Method 12): 2.17 min, 440.4 $[M\text{-}Boc+H]^+$.

**Intermediate 380:** Ethyl (*S*)-3-amino-3-(5-cyclopropyl-4-fluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00538]** A suspension of **Intermediate 379** (0.54 g, 0.96 mmol) in 4 M HCl in 1,4-dioxane (4.8 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (0.56 g). LCMS (Method 12): 2.04 min, 440.4 $[M+H]^+$.

**Intermediate 381:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00539]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 380** (0.56 g, 1.00 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.17 g, 1.50 mmol, CAS 413622-10-3), DIPEA (0.69 mL, 3.99 mmol), HOBt (0.15 g, 1.10 mmol) and EDCI (0.29 g, 1.50 mmol) in MeCN (13 mL) at RT for 16 h. Purified by flash chromatography (24 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.39 g). LCMS (Method 12): 1.98 min, 538.5 $[M+H]^+$.

**Intermediate 382:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00540]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 381** (0.48 g, 0.90 mmol), triethylamine (0.25 mL, 1.80 mmol) and methanesulfonyl chloride (0.04 mL, 0.54 mmol) in DCM (17 mL) at 0 °C for 10 min then RT for 1 h, to provide the title compound (0.56 g). LCMS (Method 12): 2.03 min, 616.5 $[M+H]^+$.

**Intermediate 383:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00541]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 382** (0.56 g, 0.77 mmol), **Intermediate 258** (0.22 g, 0.93 mmol) and $K_2CO_3$ (0.32 g, 2.32 mmol) in MeCN (13 mL) at reflux for 30 h. Purified by reverse phase chromatography (38 g C18, eluting 0-100% MeCN in 0.1% aqueous ammonia) to provide the title compound (0.18 g). LCMS (Method 11): 2.79 min, 752.8 $[M-H]^-$.

**Intermediate 384:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00542]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 383** (85 mg, 0.11 mmol) in DCE (52 mL) and Grubbs II (9.6 mg, 11 µmol) at 40 °C for 6 h. Additional Grubbs II (9.6 mg, 11 µmol) was added and heating continued at 40 °C for 18 h. Additional Grubbs II (9.6 mg, 11 µmol) was added and heating continued at 40 °C for 5 h. Purified by flash chromatography (12 g silica gel, eluting 0-6% (0.5%ammonia MeOH) in DCM) to provide the title compound (79 mg). LCMS (Method 11): 2.63 min, 726.2 $[M+H]^+$.

**Intermediate 385:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00543]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 384** (79 mg, 0.11 mmol) and 10% palladium on carbon (11.6 mg) in ethanol (7.5 mL) under a hydrogen atmosphere at RT for 6 h, to provide the title compound (68 mg). LCMS (Method 21): 5.58 min, 728.2 $[M+H]^+$.

**Intermediate 386:** Ethyl 2-((10*S*,13*S*)-1$^4$-fluoro-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-10-(2-oxo-5-(3-(pyrrolidin-1-yl)prop-1-yn-1-yl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00544]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 369** (0.10 g, 0.13 mmol), $Pd(PPh_3)_2Cl_2$ (5 mg, 7 µmol), copper(I) iodide (2 mg, 11 µmol), triethylamine (0.10 mL, 0.72 mmol) and 1-(2-propynyl)pyrrolidine (80 mg, 0.66 mmol, CAS 7223-42-9) in MeCN (2 mL) at 60 °C for 3 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (30 mg). LCMS (Method 19): 5.58 min, 734.8 $[M-H]^-$.

**Intermediate 387:** Ethyl 2-((10*S*,13*S*)-1$^4$-fluoro-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-10-(2-oxo-5-(3-(pyrrolidin-1-yl)propyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00545]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 386** (30 mg, 0.04 mmol) and 10% palladium on carbon (10 mg) in ethanol (2 mL) under a hydrogen atmosphere at RT for 22 h. Additional 10% palladium on carbon (10 mg) was added and the mixture was stirred under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (13 mg). LCMS (Method 25): 3.83 min, 742.3 $[M+H]^+$.

**Intermediate 388:** 2-Bromo-4-fluoro-3,5-dimethylphenol

**[00546]** To a stirred solution of 4-fluoro-3,5-dimethylphenol (2.64 g, 18.8 mmol, CAS 1043450-63-0) in MeCN (80 mL) was added NBS (3.35 g, 18.8 mmol) in MeCN (80 mL) dropwise at 0 °C and the mixture was stirred at 0 °C for 90 min. The mixture was concentrated under reduced pressure and the crude product was purified by dry flash chromatography (silica gel, eluting 0-5% EtOAc in petroleum ether) to provide the title compound (1.2 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 6.75 (d, 1H), 5.30 (s, 1H), 2.34 (d, 3H), 2.23 (d, 3H).

**Intermediate 389:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-3',4-difluoro-6'-hydroxy-2',4'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00547]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 377** (1.45 g, 3.04 mmol), **Intermediate 388** (0.99 g, 4.56 mmol), $K_3PO_4$ (1.94 g, 9.09 mmol), palladium acetate (68 mg, 0.30 mmol) and tricyclohexyl phosphine (0.14 g, 0.51 mmol) in toluene (28

mL) and water (9 mL) at 100 °C for 3 h. Purified by flash chromatography (40 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (1.18 g). LCMS (Method 15): 2.40 min, 390.1 $[M\text{-}Boc+H]^+$.

**Intermediate 390:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-3',4-difluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00548]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 389** (1.18 g, 2.21 mmol), $K_2CO_3$ (0.46 g, 3.31 mmol) and 5-bromopent-1-ene (0.29 mL, 2.43 mmol) in MeCN (20 mL) at reflux for 16 h. Purified by flash chromatography (24 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (1.0 g). LCMS (Method 15): 2.84 min, 458.1 $[M\text{-}Boc+H]^+$.

**Intermediate 391:** Ethyl (*S*)-3-amino-3-(5-cyclopropyl-3',4-difluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00549]** A suspension of **Intermediate 390** (1.0 g, 1.70 mmol) in 4 M HCl in 1,4-dioxane (8.5 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (1.03 g). LCMS (Method 22): 2.04 min, 458.1 $[M+H]^+$.

**Intermediate 392:** Ethyl (*S*)-3-(5-cyclopropyl-3',4-difluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00550]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 391** (0.94 g, 1.90 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.33 g, 2.84 mmol, CAS 413622-10-3), DIPEA (1.32 mL, 7.58 mmol), HOBt (0.28 g, 2.09 mmol) and EDCI (0.54 g, 2.84 mmol) in MeCN (21 mL) at RT for 16 h. Purified by flash chromatography (20 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.68 g). LCMS (Method 22): 2.00 min, 556.3 $[M+H]^+$.

**Intermediate 393:** Ethyl (*S*)-3-(5-cyclopropyl-3',4-difluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00551]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 392** (0.65 g, 1.17 mmol), triethylamine (0.33 mL, 2.34 mmol) and methanesulfonyl chloride (0.05 mL, 0.70 mmol) in DCM (23 mL) at 0 °C for 10 min then RT for 2 h, to provide the title compound (0.76 g). LCMS (Method 22): 2.04 min, 634.2 $[M+H]^+$.

**Intermediate 394:** Ethyl (*S*)-3-(5-cyclopropyl-3',4-difluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00552]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 393** (0.76 g, 1.02 mmol), **Intermediate 258** (0.29 g, 1.23 mmol) and $K_2CO_3$ (0.42 g, 3.07 mmol) in MeCN (18 mL) at reflux for 30 h. Purified by flash chromatography (20 g silica, eluting 0-5% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.23 g). LCMS (Method 15): 2.83 min, 772.4 $[M+H]^+$.

**Intermediate 395:** Ethyl 2-((10*S*,13*S*)-1$^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^5$-difluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00553]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 394** (0.23 g, 0.30 mmol) in DCE (0.14 L) and Grubbs II (26 mg, 30 µmol) at 40 °C for 6 h. Additional Grubbs II (9.6 mg, 11 µmol) was added and heating continued at 40 °C for 18 h. Additional Grubbs II (9.6 mg, 11 µmol) was added and heating continued at 40 °C for 24 h. Purified by flash chromatography (12 g silica gel, eluting 0-6% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.21 g). LCMS (Method 15): 2.65 min, 744.3 $[M+H]^+$.

**Intermediate 396:** Ethyl 2-((10*S*,13*S*)-1$^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^5$-difluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00554]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 395** (0.21 g, 0.29 mmol) and 10% palladium on carbon (30 mg) in ethanol (21 mL) under a hydrogen atmosphere at RT for 3 h, to provide the title compound (0.20 g). LCMS (Method 15): 2.68 min, 746.3 $[M+H]^+$.

**Intermediate 397:** (*R*,*E*)-*N*-(3-Bromo-2,6-difluoro-5-methylbenzylidene)-2-methylpropane-2-sulfinamide

**[00555]** Prepared in an analogous manner to **Intermediate 102** using 3-bromo-2,6-difluoro-5-methylbenzaldehyde (17.8 g, 75.7 mmol, CAS 1781530-36-6), (*R*)-2-methylpropane-2-sulfinimide (10.1 g, 83.3 mmol, CAS 196929-78-9) and titanium ethoxide (25.9 g, 0.11 mol) in THF (0.16 L) at 40 °C for 18 h, to provide the title compound (24.3 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 8.78 (s, 1H), 7.53 (dd, 1H), 2.29 (s, 3H), 1.28 (s, 9H).

**Intermediate 398:** Ethyl (*S*)-3-(3-bromo-2,6-difluoro-5-methylphenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

**[00556]** Prepared in an analogous manner to **Intermediate 104** using zinc (8.05 g, 0.12 mol), chlorotrimethylsilane (0.94 mL, 7.39 mmol) and ethyl bromoacetate (6.83 mL, 61.6 mmol) in THF (0.30 L) at 60 °C for 1 h, then **Intermediate 397** (8.33 g, 24.6 mmol) in THF (10 mL) at RT for 18 h. Run in two equal batches then purified by dry flash chromatography (silica gel,

eluting 0-40% EtOAc in petroleum ether) to provide the title compound (18.1 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.33 (dd, 1H), 5.27 – 5.24 (m, 1H), 4.32 (br s, 1H), 3.16 (dd, 1H), 2.93 (dd, 1H), 2.42 (br s, 1H), 2.23 (s, 3H), 1.22 (t, 3H), 1.16 (s, 9H) – 1H not observed.

**Intermediate 399:** Ethyl (*S*)-3-amino-3-(3-bromo-2,6-difluoro-5-methylphenyl)propanoate

**[00557]** A solution of **Intermediate 398** (14.6 g, 34.2 mmol) in ethanol (40 mL) and 4 M HCl in 1,4-dioxane (51 mL) was stirred at RT for 4 h. The mixture was concentrated under reduced pressure, dissolved in water and washed with EtOAc. The aqueous was basified with saturated $NaHCO_3$ then extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide the title compound (9.49 g). $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.45 (dd, 1H), 4.69 (t, 1H), 4.08 (q, 2H), 2.93 (dd, 1H), 2.83 (dd, 1H), 2.24 (s, 3H), 1.17 (t, 3H).

**Intermediate 400:** Ethyl (*S*)-3-(3-bromo-2,6-difluoro-5-methylphenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00558]** To a stirred suspension of **Intermediate 399** (9.49 g, 29.5 mmol) and Boc anhydride (7.71 g, 35.3 mmol) in DCM (35 mL) was added DIPEA (7.70 mL, 44.2 mmol) and the mixture stirred for 4 h at RT. The reaction mixture was diluted with DCM and washed with 1 M aqueous HCl, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by dry flash chromatography (silica gel, eluting 0-10% EtOAc in petroleum ether) to provide the title compound (10.7 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.30 (dd, 1H), 5.61 (br s, 1H), 5.31 (br s, 1H), 4.10 (q, 2H), 2.88 (dd, 1H), 2.79 (dd, 1H), 2.22 (s, 3H), 1.41 (s, 9H), 1.20 (t, 3H).

**Intermediate 401:** Ethyl (3*S*)-3-(2'-(benzyloxy)-2,4-difluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00559]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 309** (0.13 g, 0.51 mmol), **Intermediate 400** (0.20 g, 0.46 mmol), $K_3PO_4$ (0.29 g, 1.38 mmol) and XPhosPdG2 (36 mg, 0.05 mmol) in 1,4-dioxane (12.7 mL), and water (1.3 mL) at 110 °C for 1 h. Purified by flash chromatography (12 g silica gel, eluting 0-25% EtOAc in petroleum ether) to provide the title compound (0.17 g). LCMS (Method 11): 2.07 min, 454.4 $[M\text{-}Boc+H]^+$.

**Intermediate 402:** Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2,4-difluoro-2'-hydroxy-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00560]** Prepared in an analogous manner to **Intermediate 127** using **Intermediate 401** (0.58 g, 1.05 mmol), ammonium formate (1.98 g, 31.4 mmol), 10% palladium on carbon (0.11 g, 0.11 mmol) in ethanol (12 mL) at 80 °C for 16 h. Additional ammonium formate (1.98 g, 31.4 mmol) and 10% palladium on carbon (0.11 g, 0.11 mmol) was added and heating continued

for 24 h. Purified by flash chromatography (12 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.38 g). LCMS (Method 22): 1.73 min, 364.0 $[M\text{-}Boc+H]^+$.

**Intermediate 403:** Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2,4-difluoro-2',4',5-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00561]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 402** (0.67 g, 1.45 mmol), $K_2CO_3$ (0.30 g, 2.18 mmol) and 5-bromopent-1-ene (0.19 mL, 1.60 mmol) in MeCN (22 mL) at reflux for 16 h. Additional 5-bromopent-1-ene (0.05 mL, 0.44 mmol) was added and heated at reflux for 5 h. Purified by flash chromatography (24 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.63 g). LCMS (Method 22): 2.12 min, 432.1 $[M\text{-}Boc+H]^+$.

**Intermediate 404:** Ethyl (3*S*)-3-amino-3-(2,4-difluoro-2',4',5-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00562]** A suspension of **Intermediate 403** (0.63 g, 1.12 mmol) in 4 M HCl in 1,4-dioxane (5.6 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (0.65 g). LCMS (Method 22): 1.94 min, 432.1 $[M+H]^+$.

**Intermediate 405:** Ethyl (3*S*)-3-(2,4-difluoro-2',4',5-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00563]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 404** (0.65 g, 1.10 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.19 g, 1.65 mmol, CAS 413622-10-3), DIPEA (0.77 mL, 4.41 mmol), HOBt (0.16 g, 1.21 mmol) and EDCI (0.32 g, 1.65 mmol) in MeCN (15 mL) at RT for 16 h. Purified by flash chromatography (20 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.37 g). LCMS (Method 22): 1.92 min, 530.2 $[M+H]^+$.

**Intermediate 406:** Ethyl (3*S*)-3-(2,4-difluoro-2',4',5-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00564]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 405** (0.39 g, 0.74 mmol), triethylamine (0.21 mL, 1.47 mmol) and methanesulfonyl chloride (34 µL, 0.44 mmol) in DCM (14 mL) at 0 °C for 10 min then RT for 2 h, to provide the title compound (0.44 g). LCMS (Method 22): 1.96 min, 608.1 $[M+H]^+$.

**Intermediate 407:** Ethyl (3*S*)-3-(2,4-difluoro-2',4',5-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00565]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 406** (0.44 g, 0.62 mmol), **Intermediate 258** (0.17 g, 0.74 mmol) and $K_2CO_3$ (0.26 g, 1.85 mmol) in MeCN (10 mL) at reflux for 30 h. Purified by flash chromatography (20 g silica, eluting 0-5% (0.5% ammonia MeOH) in DCM) and then by reverse phase chromatography (32 g C18, 5-50% MeCN in 0.1% aqueous formic acid) to provide the title compound (90 mg). LCMS (Method 15): 2.70 min, 746.3 $[M+H]^+$.

**Intermediate 408:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^2$,$1^4$-difluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00566]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 407** (90 mg, 0.12 mmol) in DCE (55 mL) and Grubbs II (10.2 mg, 12 µmol) at 40 °C for 6 h. Additional Grubbs II (10.2 mg, 12 µmol) was added and heating continued at 40 °C for 18 h. Additional Grubbs II (10.2 mg, 12 µmol) was added and heating continued at 40 °C for 24 h. Purified by flash chromatography (12 g silica gel, eluting 0-6% 0.5%ammonia MeOH in DCM) to provide the title compound (79 mg). LCMS (Method 21): 5.22 min, 718.3 $[M+H]^+$.

**Intermediate 409:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^2$,$1^4$-difluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00567]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 408** (79 mg, 33 µmol) and 10% palladium on carbon (3.5 mg) in ethanol (7.8 mL) under a hydrogen atmosphere at RT for 3 h, to provide the title compound (73 mg). LCMS (Method 15): 2.49 min, 720.2 $[M+H]^+$.

**Intermediate 410:** Ethyl (3*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-2,4-difluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00568]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 318** (0.93 g, 1.40 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.34 g, 1.40 mmol, CAS 109919-32-6) and $K_2CO_3$ (0.58 g, 4.19 mmol) in MeCN (10 mL) at 85 °C for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.27 g). LCMS (Method 22): 2.17 min, 781.2 $[M+H]^+$.

**Intermediate 411:** Ethyl 2-((10*S*,13*S*)-10-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$-cyclopropyl-$1^2$,$1^4$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00569]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 410** (0.27 g, 0.28 mmol) in DCE (100 mL) and Grubbs II (24 mg, 28 µmol) at 40 °C for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.22 g). LCMS (Method 22): 2.09 min, 751.1 $[M+H]^+$.

**Intermediate 412:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^2$,$1^4$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00570]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 411** (0.22 g, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (19 mg, 27 µmol), copper(I) iodide (5.2 mg, 27 µmol), triethylamine (0.23 mL, 1.63 mmol) and *N*,*N*-dimethylpropargylamine (0.18 mL, 1.63 mmol, CAS 7223-38-3) in MeCN (3.9 mL) at 60 °C for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-100% EtOAc in petroleum ether), to provide the title compound (0.26 g). LCMS (Method 22): 1.99 min, 754.2 $[M+H]^+$.

**Intermediate 413:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^2$,$1^4$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00571]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 412** (0.16 g, 0.15 mmol) and 10% palladium on carbon (16 mg) in ethanol (13 mL) under a hydrogen atmosphere at RT for 3 h, to provide the title compound (0.11 g). LCMS (Method 15): 2.80 min, 760.3 $[M+H]^+$.

**Intermediate 414:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2',4'-dimethyl-5-(trifluoromethyl)-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00572]** To a solution of **Intermediate 348** (0.36 g, 0.72 mmol) in DCM (4 mL) was added phenyl triflimide (0.26 g, 0.72 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (0.28 g, 0.86 mmol) then the mixture was stirred at RT for 2 h. The mixture was diluted with water and extracted into DCM. The organic layer was washed with water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (40 g silica gel, eluting 0 – 50% EtOAc in petroleum ether) to provide the title compound (0.54 g). LCMS (Method 22): 2.03 min, 630.2 $[M-H]^-$.

**Intermediate 415:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00573]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 414** (1.37 g, 1.95 mmol), 5-hexenylboronic acid (0.37 g, 2.92 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.81 g, 5.84 mmol), palladium acetate (44 mg, 0.20 mmol) and RuPhos (0.15 g, 0.29 mmol) in

toluene (44 mL) and water (9 mL) at reflux for 3.5 h. Purified by flash chromatography (40 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (1.04 g). LCMS (Method 15): 2.95 min, 466.2 $[M\text{-}Boc+H]^+$.

**Intermediate 416:** Ethyl (*S*)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxyhex-5-enamido)propanoate

**[00574]** A suspension of **Intermediate 415** (0.52 g, 0.92 mmol) in 4 M HCl in 1,4-dioxane (2.3 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure. This was suspended in MeCN (8 mL) and (2*R*)-2-hydroxyhex-5-enoic acid (0.18 g, 1.38 mmol, CAS 612825-60-2), DIPEA (0.41 mL, 2.30 mmol), HOBt (0.15 g, 1.10 mmol) and EDCI (0.21 g, 1.10 mmol) and the mixture was stirred at RT for 16 h. The mixture was diluted with water and extracted into EtOAc. The organic layer was washed with brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (0.32 g). LCMS (Method 22): 2.15 min, 578.2 $[M+H]^+$.

**Intermediate 417:** Ethyl (*S*)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)hex-5-enamido)propanoate

**[00575]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 416** (0.32 g, 0.51 mmol), triethylamine (0.14 mL, 1.03 mmol) and methanesulfonyl chloride (60 µL, 0.77 mmol) in DCM (2.4 mL) at 0 °C for 10 min then RT for 2 h, to provide the title compound (0.38 g). LCMS (Method 22): 2.17 min, 656.1 $[M+H]^+$.

**Intermediate 418:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)hex-5-enamido)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00576]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 417** (0.34 g, 0.52 mmol), **Intermediate 258** (0.18 g, 0.77 mmol) and $K_2CO_3$ (0.21 g, 1.54 mmol) in MeCN (5.4 mL) at reflux for 16 h. Purified by flash chromatography (20 g silica, eluting 0-5% (0.5% ammonia MeOH) in DCM) and then by flash chromatography (12 g silica gel, 0-100% EtOAc in petroleum ether) to provide the title compound (0.19 g). LCMS (Method 15): 3.00 min, 794.4 $[M+H]^+$.

**Intermediate 419:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotetradecaphan-9-en-3-yl)acetate

**[00577]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 418** (0.12 g, 0.15 mmol) in DCE (7.5 mL) and Grubbs II (12.8 mg, 15 µmol) at 40 °C for 16 h. Additional

Grubbs II (6.4 mg, 7.5 μmol) was added and stirred at 40 °C for 24 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.16 g). LCMS (Method 22): 6.05 min, 766.2 $[M+H]^+$; olefin isomerisation metathesis by-products: 5.88 min, 752.2 $[M-14+H]^+$, 5.71 min, 738.2 $[M-28+H]^+$.

**Intermediate 420:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotetradecaphane-3-yl)acetate

**[00578]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 419** (0.18 g, 0.23 mmol) and 10% palladium on carbon (24 mg) in ethanol (23 mL) under a hydrogen atmosphere at RT for 6 h, to provide the title compound (0.27 g). LCMS (Method 21): 6.21 min, 768.3 $[M+H]^+$; olefin isomerisation metathesis by-products: 6.01 min, 754.2 $[M-14+H]^+$, 5.79 min, 740.2 $[M-28+H]^+$.

**Intermediate 421:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00579]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 382** (0.31 g, 0.43 mmol), **Intermediate 324** (0.14 g, 0.52 mmol) and $K_2CO_3$ (0.18 g, 1.30 mmol) in MeCN (7.3 mL) at 85 °C for 30 h. Purified by flash chromatography (20 g silica gel, eluting 0-5% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.12 g). LCMS (Method 22): 2.27 min, 780.4 $[M+H]^+$.

**Intermediate 422:** Ethyl 2-((10*S*,13*S*)-1$^5$-cyclopropyl-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00580]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 421** (70 mg, 0.09 mmol) in DCE (30 mL) and Grubbs II (7.6 mg, 9 μmol) at 40 °C for 64 h. Additional Grubbs II (7.6 mg, 9 μmol) was added then stirred at 40 °C for 16 h. Purified by flash chromatography (4 g silica gel, eluting 0-6% (0.5% ammonia MeOH) in DCM) to provide the title compound (76 mg). LCMS (Method 15): 2.81 min, 752.3 $[M+H]^+$.

**Intermediate 423:** Ethyl 2-((10*S*,13*S*)-1$^5$-cyclopropyl-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00581]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 422** (76 mg, 0.06 mmol) and 10% palladium on carbon (6.5 mg) in ethanol (13 mL) under a hydrogen

atmosphere at RT for 4 h, to provide the title compound (72 mg). LCMS (Method 15): 2.87 min, 754.3 $[M+H]^+$.

**Intermediate 424:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-4-fluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00582]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 382** (0.56 g, 0.77 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.22 g, 0.93 mmol, CAS 109919-32-6) and $K_2CO_3$ (0.32 g, 2.32 mmol) in MeCN (6 mL) at 85 °C for 16 h. Purified by flash chromatography (20 g silica gel, eluting 0-80% EtOAc in petroleum ether) to provide the title compound (0.30 g). LCMS (Method 22): 2.87 min, 763.2 $[M+H]^+$.

**Intermediate 425:** Ethyl 2-((10*S*,13*S*)-10-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$-cyclopropyl-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00583]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 424** (0.30 g, 0.38 mmol) in DCE (0.13 L) and Grubbs II (32 mg, 38 µmol) at 40 °C for 18 h. Purified by flash chromatography (12 g silica gel, eluting 10-60% EtOAc in petroleum ether) to provide the title compound (0.21 g). LCMS (Method 15): 2.74 min, 733.1 $[M+H]^+$.

**Intermediate 426:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00584]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 425** (0.22 g, 0.28 mmol), $Pd(PPh_3)_2Cl_2$ (20 mg, 28 µmol), copper(I) iodide (5.3 mg, 28 µmol), triethylamine (0.39 mL, 2.78 mmol) and *N*,*N*-dimethylpropargylamine (0.30 mL, 2.78 mmol, CAS 7223-38-3) in MeCN (3.7 mL) at 65 °C for 96 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (0.15 g). LCMS (Method 11): 2.56 min, 736.3 $[M+H]^+$.

**Intermediate 427:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00585]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 426** (0.15 g, 0.20 mmol) and 10% palladium on carbon (21 mg) in EtOAc (5 mL) under a hydrogen atmosphere at RT for 4 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (78 mg). LCMS (Method 21): 5.84 min, 742.3 $[M+H]^+$.

**Intermediate 428:** 5-(2-(Diethylamino)ethyl)-4-(trifluoromethyl)pyridin-2(1*H*)-one

**[00586]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 322** (1.16 g, 4.24 mmol), *N*,*N*-diethylamine (0.88 mL, 8.48 mmol), triethylamine (0.71 mL, 5.09 mmol) in DCM (19 mL) and 4 Å molecular sieves at RT for 2 h, then STAB (1.80 g, 8.48 mmol) at RT for 16 h. Purified by dry flash chromatography (silica gel, eluting 0-10% MeOH in DCM). The residue was dissolved in 33% HBr in acetic acid (2.78 mL, 16.1 mmol) and heated at 85 °C for 3 h then concentrated under reduced pressure. The crude was purified by catch and release chromatography (20 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.38 g). LCMS (Method 18): 0.74 min, 263.0 $[M+H]^+$.

**Intermediate 429:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00587]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 382** (0.57 g, 0.86 mmol), **Intermediate 428** (0.25 g, 0.95 mmol) and $K_2CO_3$ (0.36 g, 2.59 mmol) in MeCN (11.5 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica, eluting 0-10% (0.5% ammonia MeOH) in DCM) and then by reverse phase chromatography (15 g C18, 40-80% MeCN in 0.1% aqueous formic acid) to provide the title compound (0.32 g). LCMS (Method 21): 6.34 min, 782.3 $[M+H]^+$.

**Intermediate 430:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00588]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 429** (0.19 g, 0.07 mmol) in DCE (0.11 L) and Grubbs II (6 mg, 7 µmol) at 50 °C for 2.5 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.15 g). LCMS (Method 21): 6.05 min, 754.3 $[M+H]^+$.

**Intermediate 431:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00589]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 430** (0.15 g, 0.05 mmol) and 10% palladium on carbon (5 mg) in MeOH (24 mL) under a hydrogen atmosphere at RT for 2 h. Purified by flash chromatography (4 g silica gel, eluting 5-10% MeOH in DCM), to provide the title compound (0.13 g). LCMS (Method 15): 2.96 min, 756.3 $[M+H]^+$.

**Intermediate 432:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-2',4'-dimethyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00590]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 378** (3.65 g, 5.43 mmol), phenyl triflimide (1.91 g, 5.34 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (2.09 g, 6.41 mmol) in DCM (40 mL) at RT for 18 h. Purified by flash chromatography (80 g silica gel, eluting 0–40% EtOAc in petroleum ether) to provide the title compound (3.0 g). LCMS (Method 22): 2.16 min, 602.2 $[M-H]^-$.

**Intermediate 433:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00591]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 432** (3.00 g, 4.97 mmol), 5-hexenylboronic acid (0.95 g, 7.46 mmol, CAS 1072952-16-9), $K_2CO_3$ (2.06 g, 14.9 mmol), palladium acetate (0.11 g, 0.50 mmol) and RuPhos (0.35 g, 0.75 mmol) in toluene (97 mL) and water (19 mL) at reflux for 18 h. Purified by flash chromatography (80 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (2.6 g). LCMS (Method 15): 3.05 min, 438.1 $[M-Boc+H]^+$.

**Intermediate 434:** Ethyl (*S*)-3-amino-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00592]** A suspension of **Intermediate 433** (2.82 g, 4.67 mmol) in 4 M HCl in 1,4-dioxane (12 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (2.21 g). LCMS (Method 15): 2.86 min, 438.1 $[M+H]^+$.

**Intermediate 435:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00593]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 434** (1.99 g, 4.20 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.73 g, 6.30 mmol, CAS 413622-10-3), DIPEA (2.24 mL, 12.6 mmol), HOBt (0.57 g, 4.20 mmol) and EDCI (0.97 g, 5.04 mmol) in MeCN (25 mL) at RT for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (1.9 g). LCMS (Method 11): 2.63 min, 536.3 $[M+H]^+$.

**Intermediate 436:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00594]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 435** (0.50 g, 0.93 mmol), triethylamine (0.26 mL, 1.87 mmol) and methanesulfonyl chloride (87 µL, 1.12 mmol) in DCM (20 mL) at 0 °C for 10 min then RT for 1 h. Cooled to 0 °C and additional

triethylamine (65 µL, 0.47 mmol) and methanesulfonyl chloride (22 µL, 0.28 mmol) then RT for 1 h, to provide the title compound (0.63 g). LCMS (Method 15): 2.87 min, 614.2 $[M+H]^+$.

**Intermediate 437:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00595]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 436** (0.63 g, 0.76 mmol), **Intermediate 258** (0.27 g, 1.15 mmol) and $K_2CO_3$ (0.32 g, 2.29 mmol) in MeCN (9.4 mL) at reflux for 16 h. Purified by flash chromatography (20 g silica, eluting 0-5% (0.5% ammonia MeOH) in DCM) and then by flash chromatography (40 g silica gel, 0-10% MeOH in DCM) to provide the title compound (0.22 g). LCMS (Method 15): 3.02 min, 752.3 $[M+H]^+$.

**Intermediate 438:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00596]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 437** (0.22 g, 0.29 mmol) in DCE (95 mL) and Grubbs II (24 mg, 29 µmol) at 40 °C for 18 h. Additional Grubbs II (24 mg, 29 µmol) was added and stirred at 40 °C for 5 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.15 g). LCMS (Method 11): 2.85 min, 722.6 $[M-H]^-$ $M+H]^+$; isomerised olefin metathesis by product: 2.73 min 710.3 $[M-14+H]^+$.

**Intermediate 439:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00597]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 438** (0.14 g, 0.10 mmol) and 10% palladium on carbon (10 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (4 g silica gel, eluting 5-10% MeOH in DCM), to provide the title compound (0.13 g). LCMS (Method 15): 2.97 min, 726.3 $[M+H]^+$; isomerised olefin metathesis by product: 2.87 min 712.3 $[M-14+H]^+$.

**Intermediate 440:** 2-Fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzaldehyde

**[00598]** Prepared in an analogous manner to **Intermediate 2** using 5-bromo-2-fluoro-3-(trifluoromethyl)benzaldehyde (0.50 g, 1.85 mmol, CAS 1291487-26-7), bis(pinacolato)diboron (0.56 g, 2.21 mmol), potassium acetate (0.36 g, 3.69 mmol) and Pd(dppf)$Cl_2$ (75 mg, 0.05 mmol) in 1,4-dioxane (20 mL) at 90 °C for 2 h. Purified by flash

chromatography (silica gel, eluting 0-5% MeOH in DCM) to provide the title compound (0.43 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 10.28 (s, 1H), 8.39 (dd, 1H), 8.16 (dd, 1H), 1.27 (s, 12H).

**Intermediate 441:** 4,4'-Difluoro-2'-hydroxy-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carbaldehyde

**[00599]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 440** (1.20 g, 3.77 mmol), 2-bromo-5-fluoro-3-methylphenol (0.70 g, 3.42 mmol, CAS 1807192-21-7), $K_3PO_4$ (1.45 g, 6.85 mmol), palladium acetate (77 mg, 0.34 mmol) and tricyclohexyl phosphine (96 mg, 0.34 mmol) in toluene (9 mL) and water (4.6 mL) at 85 °C for 3 h. Additional palladium acetate (77 mg, 0.34 mmol) and tricyclohexyl phosphine (96 mg, 0.34 mmol) were added and heating continued at 85 °C for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.45 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 10.26 (s, 1H), 7.87 – 7.80 (m, 1H), 7.70 – 7.63 (m, 1H), 6.33 (d, 1H), 6.25 – 6.20 (m, 1H), 2.14 (s, 3H) – OH not observed.

**Intermediate 442:** (*R*,*E*)-*N*-((4,4'-Difluoro-2'-hydroxy-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methylene)-2-methylpropane-2-sulfinamide

**[00600]** Prepared in an analogous manner to **Intermediate 102** using **Intermediate 441** (0.75 g, 2.32 mmol), (*R*)-2-methylpropane-2-sulfinimide (0.31 g, 2.56 mmol) and titanium ethoxide (0.80 g, 3.49 mol) in THF (20 mL) at 40 °C for 2 h, to provide the title compound (0.91 g). LCMS (Method 22): 1.85 min, 418.2 $[M-H]^-$.

**Intermediate 443:** (*R*,*E*)-*N*-((4,4'-Difluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methylene)-2-methylpropane-2-sulfinamide

**[00601]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 442** (0.91 g, 2.17 mmol), $K_2CO_3$ (0.36 g, 2.61 mmol) and 5-bromopent-1-ene (0.28 mL, 2.39 mmol) in MeCN (14.5 mL) at reflux for 4 h. Purified by flash chromatography (24 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.81 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 8.95 (s, 1H), 8.02 (dd, 1H), 7.61 (dd, 1H), 6.63 (dd, 1H), 6.54 (dd, 1H), 5.73 – 5.64 (m, 1H), 4.94 – 4.89 (m, 2H), 3.87 (t, 2H), 2.11 (s, 3H), 2.01 – 1.96 (m, 2H), 1.71 – 1.65 (m, 2H), 1.26 (s, 9H).

**Intermediate 444:** Ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,4'-difluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00602]** Prepared in an analogous manner to **Intermediate 104** using zinc (0.36 g, 5.46 mmol), chlorotrimethylsilane (28 µL, 0.22 mmol) and ethyl bromoacetate (0.30 mL, 2.73 mmol) in THF (6.8 mL) at 60 °C for 1 h, then **Intermediate 443** (0.53 g, 1.09 mmol) in THF (4.1 mL) at RT for 2 h. Purified by flash chromatography (40 g silica gel, eluting 0-80% EtOAc in petroleum ether) to provide the title compound (0.29 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.38 (d,

2H), 6.58 (dd, 1H), 6.50 (dd, 1H), 5.72 – 5.60 (m, 1H), 5.11 (q, 1H), 4.95 – 4.85 (m, 2H), 4.81 (d, 1H), 4.13 – 4.04 (m, 2H), 3.83 (t, 2H), 3.05 – 2.92 (m, 2H), 2.03 (s, 3H), 1.98 – 1.91 (m, 2H), 1.69 – 1.56 (m, 2H), 1.21 – 1.17 (m, 11H) – NH not observed.

**Intermediate 445:** Ethyl (*S*)-3-amino-3-(4,4'-difluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00603]** A suspension of **Intermediate 444** (0.29 g, 0.50 mmol) in 4 M HCl in 1,4-dioxane (2.5 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure and purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.22 g). LCMS (Method 15): 2.59 min, 472.1 $[M+H]^+$.

**Intermediate 446:** Ethyl (*S*)-3-(4,4'-difluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00604]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 445** (0.21 g, 0.45 mmol), (2*R*)-2-hydroxypent-4-enoic acid (78 mg, 0.67 mmol, CAS 413622-10-3), DIPEA (0.23 mL, 1.34 mmol), HOBt (67 mg, 0.49 mmol) and EDCI (0.10 g, 0.67 mmol) in MeCN (6 mL) at RT for 16 h. Purified by flash chromatography (25 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (0.22 g). LCMS (Method 15): 2.58 min, 570.1 $[M+H]^+$.

**Intermediate 447:** Ethyl (*S*)-3-(4,4'-difluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00605]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 446** (0.22 g, 0.38 mmol), triethylamine (0.11 mL, 0.76 mmol) and methanesulfonyl chloride (44 µL, 0.57 mmol) in DCM (3.6 mL) at 0 °C for 1 h, to provide the title compound (0.25 g). LCMS (Method 15): 2.03 min, 648.1 $[M+H]^+$.

**Intermediate 448:** Ethyl (*S*)-3-(4,4'-difluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00606]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 447** (0.25 g, 0.36 mmol), **Intermediate 324** (0.10 g, 0.39 mmol) and $K_2CO_3$ (0.15 g, 1.07 mmol) in MeCN (5 mL) at 85 °C for 18 h. Purified by flash chromatography (20 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM) then reverse phase chromatography (38 g C18, eluting 40-70% MeCN in 0.1% aqueous formic acid) to provide the title compound (97 mg). $^1$H NMR (400 MHz; $CDCl_3$) δ: 8.01 (d, 1H), 7.67 (s, 1H), 7.42 – 7.36 (m, 2H), 6.81 (s, 1H), 6.60 – 6.49 (m, 2H),

5.65 – 5.60 (m, 2H), 4.96 – 4.88 (m, 3H), 4.01 – 3.91 (m, 2H), 3.83 (t, 2H), 2.88 – 2.81 (m, 2H), 2.78 – 2.69 (m, 4H), 2.66 – 2.50 (m, 8H), 2.03 (s, 3H), 1.96 (q, 2H), 1.82 – 1.78 (m, 4H), 1.70 – 1.63 (m, 2H), 1.09 (t, 3H) – NH not observed.

**Intermediate 449:** Ethyl 2-((10*S*,13*S*)-1$^4$,2$^4$-difluoro-2$^6$-methyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00607]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 448** (97 mg, 0.11 mmol) in DCE (57 mL) and Grubbs II (9.7 mg, 11 µmol) at 50 °C for 2.5 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (54 mg). LCMS (Method 15): 2.79 min, 784.2 $[M+H]^+$.

**Intermediate 450:** Ethyl 2-((10*S*,13*S*)-1$^4$,2$^4$-difluoro-2$^6$-methyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00608]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 449** (54 mg, 0.04 mmol) and 10% palladium on carbon (4.2 mg) in ethanol (1 mL) under a hydrogen atmosphere at RT for 2 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (51 mg). LCMS (Method 15): 2.84 min, 786.3 $[M+H]^+$.

**Intermediate 451:** 6-(Cyclopent-1-en-1-yl)-4-methylbenzo[*d*]oxazol-2(3*H*)-one

**[00609]** Prepared in an analogous manner to **Intermediate 3** using 6-bromo-4-methyl-3*H*-1,3-benzoxazol-2-one (4.0 g, 17.5 mmol, CAS 868707-63-5), cyclopenten-1-ylboronic acid (2.36 g, 21.1 mmol, CAS 850036-28-1), $Na_2CO_3$ (5.58 g, 52.6 mmol) and $Pd(dppf)Cl_2$ (0.32 g, 0.44 mmol) in 1,4-dioxane (96 mL), and water (48 mL) at 80 °C for 2 h. Purified by flash chromatography (25 g silica gel, eluting 20-25% EtOAc in petroleum ether) to provide the title compound (2.0 g). $^1$H NMR (400 MHz; DMSO-$d_6$) δ: 11.67 (s, 1H), 7.22 (d, 1H), 7.06 (s, 1H), 6.23 – 6.17 (m, 1H), 2.67 – 2.57 (m, 2H), 2.50 – 2.42 (m, 2H), 2.28 (s, 3H), 2.01 – 1.88 (m, 2H).

**Intermediate 452:** 6-Cyclopentyl-4-methylbenzo[*d*]oxazol-2(3*H*)-one

**[00610]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 451** (2.0 g, 9.29 mmol) and 10% palladium on carbon (0.49 g) in THF (0.11 L), IPA (15 mL) and water (1.5 mL) under a hydrogen atmosphere at RT for 18 h, to provide the title compound (1.81 g). LCMS (Method 6): 1.42 min, 216.1 $[M-H]^-$.

**Intermediate 453:** *tert*-Butyl 6-cyclopentyl-4-methyl-2-oxobenzo[d]oxazole-3(2*H*)-carboxylate

**[00611]** To a stirred suspension of **Intermediate 452** (1.81 g, 8.33 mmol) and Boc anhydride (2.0 g, 9.16 mmol) in THF (45 mL) was added DMAP (51 mg, 0.42 mmol) and the mixture stirred for 18 h at RT. The reaction mixture was diluted with1 M aqueous HCl and extracted with EtOAc. The organic layer was washed with, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (2.7 g). LCMS (Method 6): 2.02 min, 340.0 $[M+Na]^+$.

**Intermediate 454:** *tert*-Butyl (4-cyclopentyl-2-hydroxy-6-methylphenyl)carbamate

**[00612]** To a stirred solution of **Intermediate 453** (2.7 g, 8.08 mmol) in MeOH (44 mL) at 0 °C was added $K_2CO_3$ (1.12 g, 8.08 mmol) then the mixture stirred at RT for 2 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (2.6 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.98 (s, 1H), 6.78 (d, 1H), 6.64 (d, 1H), 6.22 (s, 1H), 2.88 (tt, 1H), 2.23 (s, 3H), 2.05 – 1.94 (m, 2H), 1.83 – 1.73 (m, 2H), 1.71 – 1.60 (m, 2H), 1.60 – 1.49 (m, 11H).

**Intermediate 455:** 2-Amino-5-cyclopentyl-3-methylphenol

**[00613]** A suspension of **Intermediate 454** (2.6 g, 7.67 mmol) in 4 M HCl in 1,4-dioxane (19.2 mL) was stirred at RT for 5 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (40 g silica gel, eluting 15-60% EtOAc in petroleum ether) to provide the title compound (0.97 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 6.59 (s, 1H), 6.53 (d, 1H), 2.83 (tt, 1H), 2.19 (s, 3H), 2.04 – 1.95 (m, 2H), 1.81 – 1.72 (m, 2H), 1.70 – 1.59 (m, 2H), 1.56 – 1.46 (m, 2H) – 3H not observed.

**Intermediate 456:** 5-Cyclopentyl-2-iodo-3-methylphenol

**[00614]** A solution of **Intermediate 455** (0.45 g, 2.35 mmol) in 2 M aqueous HCl (3.53 mL) and MeCN (6.5 mL) was stirred at RT for 10 min then cooled to 0 °C before a solution of sodium nitrite (0.16 g, 2.35 mmol) in water (2.6 mL) was added. The mixture was stirred at 0 °C for 1.5 h, then potassium iodide (1.95 g, 11.8 mmol) was added and the mixture heated at 80 °C for 2.5 h. The reaction was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with 10% aqueous sodium thiosulfate, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (24 g, silica, 0–20% EtOAc in petroleum ether) to provide the title compound (0.43 g). LCMS (Method 6): 1.78 min, 301.2 $[M-H]^-$.

**Intermediate 457:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-cyclopentyl-5-cyclopropyl-4-fluoro-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00615]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 377** (1.55 g, 2.63 mmol), **Intermediate 456** (0.95 g, 3.16 mmol), $K_3PO_4$ (1.11 g, 5.26 mmol), palladium acetate (59 mg, 0.26 mmol) and tricyclohexyl phosphine (74 mg, 0.26 mmol) in toluene (23 mL) and water (3 mL) at 100 °C for 3 h. Purified by flash chromatography (40 g silica gel, eluting 0-25% EtOAc in petroleum ether) to provide the title compound (0.91 g). LCMS (Method 22): 2.12 min, 426.1 $[M\text{-}Boc+H]^+$.

**Intermediate 458:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-cyclopentyl-5-cyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00616]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 457** (0.91 g, 1.56 mmol), $K_2CO_3$ (0.32 g, 2.34 mmol) and 5-bromopent-1-ene (0.20 mL, 1.72 mmol) in MeCN (10 mL) at reflux for 16 h. Additional $K_2CO_3$ (54 mg, 0.25 mmol) and 5-bromopent-1-ene (46 µL, 0.31 mmol) and stirred at 85 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.85 g). LCMS (Method 25): 3.93 min, 592.5 $[M-H]^-$.

**Intermediate 459:** Ethyl (*S*)-3-amino-3-(4'-cyclopentyl-5-cyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00617]** A suspension of **Intermediate 458** (0.85 g, 1.28 mmol) in 4 M HCl in 1,4-dioxane (3.2 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.60 g). LCMS (Method 22): 2.29 min, 494.2 $[M+H]^+$.

**Intermediate 460:** Ethyl (*S*)-3-(4'-cyclopentyl-5-cyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00618]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 459** (0.60 g, 1.16 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.13 g, 1.16 mmol, CAS 413622-10-3), DIPEA (0.62 mL, 3.47 mmol), HOBt (0.16 g, 1.16 mmol) and EDCI (0.27 g, 1.39 mmol) in MeCN (10 mL) at RT for 18 h. Purified by flash chromatography (25 g silica gel, eluting 20-60% EtOAc in petroleum ether) to provide the title compound (0.64 g). LCMS (Method 15): 2.93 min, 592.3 $[M+H]^+$.

**Intermediate 461:** Ethyl (*S*)-3-(4'-cyclopentyl-5-cyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00619]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 460** (0.67 g, 0.91 mmol), triethylamine (0.25 mL, 1.82 mmol) and methanesulfonyl chloride (0.11 mL, 1.36 mmol) in DCM (6 mL) at 0 °C for 10 min, then RT for 4 h to provide the title compound (0.62 g). LCMS (Method 15): 2.96 min, 668.4 $[M-H]^-$.

**Intermediate 462:** Ethyl (*S*)-3-(4'-cyclopentyl-5-cyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00620]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 461** (0.52 g, 0.73 mmol), **Intermediate 258** (0.21 g, 0.88 mmol) and $K_2CO_3$ (0.30 g, 2.20 mmol) in MeCN (7 mL) at reflux for 18 h. Purified by flash chromatography (25 g silica gel, 1.5-4% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.14 g). LCMS (Method 18): 1.95 min, 808.4 $[M+H]^+$.

**Intermediate 463:** Ethyl 2-((10*S*,13*S*)-$2^4$-cyclopentyl-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00621]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 462** (0.14 g, 0.17 mmol) in DCE (75 mL) and Grubbs II (14.7 mg, 17 µmol) at 50 °C for 2 h. Additional Grubbs II (14.7 mg, 17 µmol) was added and stirred at 50 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-8% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.11 g). LCMS (Method 15): 3.00 min, 780.4 $[M+H]^+$.

**Intermediate 464:** Ethyl 2-((10*S*,13*S*)-$2^4$-cyclopentyl-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00622]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 463** (0.11 g, 0.14 mmol) and 10% palladium on carbon (15 mg) in ethanol (5 mL) under a hydrogen atmosphere at RT for 3 h, to provide the title compound (90 mg). LCMS (Method 15): 3.02 min, 782.3 $[M+H]^+$.

**Intermediate 465:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(3-(diethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00623]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 425** (0.19 g, 0.24 mmol), $Pd(PPh_3)_2Cl_2$ (16.8 mg, 24 µmol), copper(I) iodide (4.6 mg, 24 µmol), triethylamine (0.33 mL, 2.40 mmol) and *N*,*N*-diethylpropargylamine (0.34 mL, 2.40 mmol, CAS 4079-68-9) in MeCN (3.2 mL) at 65 °C for 18 h. Additional $Pd(PPh_3)_2Cl_2$ (8.4 mg, 12 µmol), copper(I) iodide (2.3 mg, 12 µmol), triethylamine (0.17 mL, 1.20 mmol) and *N*,*N*-diethylpropargylamine (0.17 mL, 1.20 mmol, CAS 4079-68-9) were added and heated at 65 °C for 24 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (0.29 g). LCMS (Method 15): 2.85 min, 764.3 $[M+H]^+$.

**Intermediate 466:** Ethyl 2-((10*S*,13*S*)-1$^5$-cyclopropyl-10-(5-(3-(diethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00624]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 465** (0.29 g, 0.07 mmol) and 10% palladium on carbon (7 mg) in ethanol (4 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM), to provide the title compound (14 mg). LCMS (Method 15): 3.12 min, 770.3 $[M+H]^+$.

**Intermediate 467:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00625]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 436** (0.70 g, 0.93 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.29 g, 1.21 mmol, CAS 109919-32-6) and $K_2CO_3$ (0.39 g, 2.80 mmol) in MeCN (44 mL) at reflux for 16 h. Purified by flash chromatography (20 g silica, eluting 0-5% (0.5% ammonia MeOH) in DCM) and then by flash chromatography (20 g silica gel, 0-80% EtOAc in petroleum ether) to provide the title compound (0.27 g). LCMS (Method 15): 3.00 min, 761.2 $[M+H]^+$.

**Intermediate 468:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00626]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 467** (0.27 g, 0.35 mmol) in DCE (0.12 L) and Grubbs II (30 mg, 35 µmol) at 40 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.14 g). LCMS (Method 15): 2.93 min, 733.1 $[M+H]^+$.

**Intermediate 469:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00627]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 468** (0.13 g, 0.18 mmol), $Pd(PPh_3)_2Cl_2$ (13 mg, 18 µmol), copper(I) iodide (3.5 mg, 18 µmol), triethylamine (0.25 mL, 1.82 mmol) and *N*,*N*-dimethylpropargylamine (0.20 mL, 1.81 mmol, CAS 7223-38-3) in MeCN (2.4 mL) at 65 °C for 18 h. Additional $Pd(PPh_3)_2Cl_2$ (13 mg, 18 µmol), copper(I) iodide (3.5 mg, 18 µmol), and *N*,*N*-dimethylpropargylamine (0.20 mL, 1.81 mmol) were added and heating continued at 65 °C for 24 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM), to provide the title compound (48 mg). LCMS (Method 15): 2.88 min, 734.3 $[M+H]^+$.

**Intermediate 470:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00628]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 469** (48 mg, 0.07 mmol) and 10% palladium on carbon (7 mg) in ethanol (5 mL) under a hydrogen atmosphere at RT for 16 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (24 mg). LCMS (Method 15): 2.99 min, 740.3 $[M+H]^+$.

**Intermediate 471:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-cyclopropyl-4-fluoro-2',5-dimethyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00629]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 338** (1.30 g, 2.76 mmol), phenyl triflimide (0.99 g, 3.31 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (1.08 g, 3.31 mmol) in DCM (21 mL) at RT for 16 h. Purified by flash chromatography (12 g silica gel, eluting 0–20% EtOAc in petroleum ether) to provide the title compound (1.47 g). LCMS (Method 15): 2.77 min, 504.2 $[M\text{-}Boc+H]^+$.

**Intermediate 472:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00630]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 471** (1.47 g, 2.43 mmol), 5-hexenylboronic acid (0.47 g, 3.64 mmol, CAS 1072952-16-9), $K_2CO_3$ (1.01 g, 7.29 mmol), palladium acetate (54 mg, 0.24 mmol) and RuPhos (0.17 g, 0.36 mmol) in toluene (47 mL) and water (10 mL) at 100 °C for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (1.0 g). LCMS (Method 22): 2.30 min, 438.1 $[M\text{-}Boc+H]^+$.

**Intermediate 473:** Ethyl (*S*)-3-amino-3-(4'-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00631]** A suspension of **Intermediate 472** (1.03 g, 1.82 mmol) in 4 M HCl in 1,4-dioxane (9.1 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (1.02 g). LCMS (Method 15): 2.82 min, 438.2 $[M+H]^+$.

**Intermediate 474:** Ethyl (*S*)-3-(4'-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00632]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 473** (1.02 g, 1.67 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.29 g, 2.51 mmol, CAS 413622-10-3), DIPEA (1.17 mL, 6.69 mmol), HOBt (0.25 g, 1.84 mmol) and EDCI (0.48 g, 2.51 mmol) in MeCN (22 mL) at RT for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-50%

EtOAc in petroleum ether) to provide the title compound (0.73 g). LCMS (Method 22): 2.16 min, 536.2 $[M+H]^+$.

**Intermediate 475:** Ethyl (*S*)-3-(4'-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00633]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 474** (0.73 g, 1.36 mmol), triethylamine (0.38 mL, 2.71 mmol) and methanesulfonyl chloride (63 µL, 0.81 mmol) in DCM (26 mL) at 0 °C for 10 min, then RT for 2 h to provide the title compound (0.80 g). LCMS (Method 22): 2.17 min, 614.3 $[M+H]^+$.

**Intermediate 476:** Ethyl (*S*)-3-(4'-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00634]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 475** (0.80 g, 1.10 mmol), **Intermediate 258** (0.31 g, 1.32 mmol) and $K_2CO_3$ (0.46 g, 3.31 mmol) in MeCN (19 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, 0-6% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.31 g). LCMS (Method 22): 2.30 min, 752.3 $[M+H]^+$.

**Intermediate 477:** Ethyl 2-((3*S*,6*S*)-$1^4$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00635]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 476** (0.31 g, 0.41 mmol) in DCE (0.19 L) and Grubbs II (35 mg, 41 µmol) at 40 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-6% MeOH in DCM) to provide the title compound (0.30 g). LCMS (Method 15): 2.93 min, 724.2 $[M+H]^+$; olefin isomerisation metathesis by-product: 2.81 min, 710.2 $[M-14+H]^+$.

**Intermediate 478:** Ethyl 2-((3*S*,6*S*)-$1^4$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00636]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 477** (0.30 g, 0.42 mmol) and 10% palladium on carbon (44 mg) in ethanol (30 mL) under a hydrogen atmosphere at RT for 3 h, to provide the title compound (0.25 g). LCMS (Method 15): 2.92 min, 726.3 $[M+H]^+$; olefin isomerisation metathesis by-product: 2.82 min, 712.3 $[M-14+H]^+$.

**Intermediate 479:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00637]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 436** (0.67 g, 1.00 mmol), **Intermediate 200** (0.20 g, 1.01 mmol) and $K_2CO_3$ (0.42 g, 3.00 mmol) in MeCN (13 mL) at reflux for 16 h. Purified by flash chromatography (20 g silica, eluting 0-5% (0.5% ammonia MeOH) in DCM) and then by flash chromatography (40 g silica gel, 0-10% MeOH in DCM) to provide the title compound (0.25 g). LCMS (Method 15): 2.88 min, 702.3 $[M+H]^+$.

**Intermediate 480:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00638]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 479** (0.25 g, 0.35 mmol) in DCE (0.14 L) and Grubbs II (30 mg, 35 µmol) at 50 °C for 2.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.14 g). LCMS (Method 15): 2.78 min, 674.3 $[M+H]^+$.

**Intermediate 481:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00639]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 480** (0.14 g, 0.16 mmol) and 10% palladium on carbon (16 mg) in ethanol (8 mL) under a hydrogen atmosphere at RT for 3 h, to provide the title compound (0.14 g). LCMS (Method 15): 2.82 min, 676.3 $[M+H]^+$.

**Intermediate 482:** *tert*-Butyl (2-(benzyloxy)-4-bromo-6-methylphenyl)carbamate

**[00640]** Prepared in an analogous manner to **Intermediate 6** using *tert*-butyl (4-bromo-2-hydroxy-6-methylphenyl)carbamate (9.16 g, 30.3 mmol, CAS 2757912-18-6), $K_2CO_3$ (5.45 g, 39.4 mmol) and benzyl bromide (5.70 mL, 33.3 mmol) in MeCN (0.13 L) at 65 °C for 18 h, to provide the title compound (11.8 g). LCMS (Method 22): 1.87 min, 392.1 $[M+H]^+$.

**Intermediate 483:** *tert*-Butyl (2-(benzyloxy)-4-cyclopropyl-6-methylphenyl)carbamate

**[00641]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 482** (11.8 g, 30.2 mmol), cyclopropaneboronic acid (6.48 g, 75.4 mmol), $K_3PO_4$ (12.8 g, 60.3 mmol), palladium acetate (0.68 g, 3.02 mmol) and tricyclohexyl phosphine (0.85 g, 3.02 mmol) in toluene (0.21 L) and water (86 mL) at 110 °C for 18 h. Purified by dry flash chromatography (silica gel, eluting 0-10% EtOAc in petroleum ether) to provide the title compound (9.68 g). LCMS (Method 22): 1.97 min, 352.3 $[M-H]^-$.

**Intermediate 484:** 2-(Benzyloxy)-4-cyclopropyl-6-methylaniline

**[00642]** A suspension of **Intermediate 483** (11.3 g, 32.0 mmol) in 4 M HCl in 1,4-dioxane (32 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure and the

residue basified with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organics were washed with brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (7.87 g). LCMS (Method 22): 1.82 min, 254.1 $[M+H]^+$.

**Intermediate 485:** 2-Amino-5-cyclopropyl-3-methylphenol

**[00643]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 484** (1.00 g, 3.95 mmol) and 10% palladium on carbon (0.21 g) in EtOAc (40 mL) under a hydrogen atmosphere at RT for 2.5 h. Purified by flash chromatography (25 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.53 g). LCMS (Method 22): 1.29 min, 164.0 $[M+H]^+$.

**Intermediate 486:** 5-Cyclopropyl-2-iodo-3-methylphenol

**[00644]** Prepared in an analogous manner to **Intermediate 456** using **Intermediate 485** (0.53 g, 3.25 mmol) in 2 M aqueous HCl (4.9 mL) and MeCN (8 mL) was stirred at RT for 20 min then sodium nitrite (0.22 g, 3.25 mmol) in water (2.8 mL) at 0 °C for 0.5 h, then potassium iodide (2.70 g, 16.3 mmol) at 80 °C for 7.5 h. Purified by flash chromatography (25 g, silica, 0–20% EtOAc in petroleum ether) to provide the title compound (0.63 g). LCMS (Method 22): 1.61 min, 273.0 $[M-H]^-$.

**Intermediate 487**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4',5-dicyclopropyl-4-fluoro-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00645]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 486** (0.51 g, 1.87 mmol), **Intermediate 377** (1.0 g, 1.70 mmol), $K_3PO_4$ (0.72 g, 3.39 mmol), palladium acetate (38 mg, 0.17 mmol) and tricyclohexyl phosphine (48 mg, 0.17 mmol) in toluene (15 mL) and water (1.2 mL) at 100 °C for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.57 g). LCMS (Method 22): 1.98 min, 496.2 $[M-H]^-$.

**Intermediate 488:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4',5-dicyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00646]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 487** (0.86 g, 1.73 mmol), $K_2CO_3$ (0.36 g, 2.60 mmol) and 5-bromopent-1-ene (0.23 mL, 1.91 mmol) in MeCN (11 mL) at reflux for 16 h. Additional $K_2CO_3$ (29 mg, 0.21 mmol) and 5-bromopent-1-ene (21 µL, 0.17 mmol) and stirred at 85 °C for 2 h. Purified by flash chromatography (25 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.98 g). LCMS (Method 15): 2.91 min, 466.2 $[M-Boc+H]^+$.

**Intermediate 489:** Ethyl (*S*)-3-amino-3-(4',5-dicyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00647]** A suspension of **Intermediate 488** (0.98 g, 1.66 mmol) in 4 M HCl in 1,4-dioxane (4.2 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (1.02 g). LCMS (Method 22): 2.13 min, 466.2 $[M+H]^+$.

**Intermediate 490:** Ethyl (*S*)-3-(4',5-dicyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00648]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 489** (0.84 g, 1.66 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.19 g, 1.66 mmol, CAS 413622-10-3), DIPEA (0.89 mL, 4.99 mmol), HOBt (0.22 g, 1.66 mmol) and EDCI (0.38 g, 2.00 mmol) in MeCN (14 mL) at RT for 16 h. Additional (2*R*)-2-hydroxypent-4-enoic acid (64 mg, 0.55 mmol), DIPEA (0.30 mL, 1.70 mmol), HOBt (74 mg, 0.55 mmol) and EDCI (0.13 g, 0.67 mmol) were added and stirred at RT for 24 h. Purified by flash chromatography (40 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.74 g). LCMS (Method 15): 2.68 min, 564.2 $[M+H]^+$.

**Intermediate 491:** Ethyl (*S*)-3-(4',5-dicyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00649]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 490** (0.66 g, 0.95 mmol), triethylamine (0.27 mL, 1.91 mmol) and methanesulfonyl chloride (0.11 mL, 1.43 mmol) in DCM (7 mL) at 0 °C for 10 min, then RT for 1 h to provide the title compound (0.77 g). LCMS (Method 15): 2.73 min, 642.3 $[M+H]^+$.

**Intermediate 492:** Ethyl (*S*)-3-(4',5-dicyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00650]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 491** (0.74 g, 0.96 mmol), **Intermediate 258** (0.27 g, 1.15 mmol) and $K_2CO_3$ (0.40 g, 2.89 mmol) in MeCN (9 mL) at reflux for 18 h. Additional **Intermediate 258** (0.20 g, 0.88 mmol) was added and refluxed for 18 h. Purified by flash chromatography (40 g silica gel, 0-3% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.29 g). LCMS (Method 15): 2.89 min, 780.4 $[M+H]^+$.

**Intermediate 493:** Ethyl 2-((10*S*,13*S*)-$1^5$,$2^4$-dicyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00651]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 492** (0.14 g, 0.18 mmol) in DCE (78 mL) and Grubbs II (15 mg, 18 µmol) at 50 °C for 4 h. Additional Grubbs II (76 mg, 90 µmol) was added and stirred at 40 °C for 16 h. Purified by flash

chromatography (40 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.24 g). LCMS (Method 21): 5.72 min, 752.3 $[M+H]^+$: olefin isomerisation metathesis product: 5.60 min, 738.2 $[M-14+H]^+$.

**Intermediate 494:** Ethyl 2-((10*S*,13*S*)-$1^5$,$2^4$-dicyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00652]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 493** (0.24 g, 0.18 mmol) and 10% palladium on carbon (34 mg) in ethanol (3 mL) under a hydrogen atmosphere at RT for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-4% (0.5% ammonia MeOH) in DCM) to provide the title compound (76 mg). LCMS (Method 21): 5.82 min, 754.3 $[M+H]^+$; olefin isomerisation metathesis product: 5.70 min, 740.3 $[M-14+H]^+$.

**Intermediate 495**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-6'-hydroxy-2',3',4'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00653]** Prepared in an analogous manner to **Intermediate 3** using 2-bromo-3,4,5-trimethylphenol (0.54 g, 2.40 mmol, CAS 87025-09-0), **Intermediate 377** (1.06 g, 2.00 mmol), $K_3PO_4$ (0.85 g, 4.00 mmol), palladium acetate (45 mg, 0.20 mmol) and tricyclohexyl phosphine (56 mg, 0.20 mmol) in toluene (14 mL) and water (1.5 mL) at 100 °C for 16 h. Purified by flash chromatography (12 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.63 g). LCMS (Method 22): 1.98 min, 484.3 $[M-H]^-$.

**Intermediate 496:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-2',3',4'-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00654]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 495** (1.02 g, 1.87 mmol), $K_2CO_3$ (0.39 g, 2.80 mmol) and 5-bromopent-1-ene (0.24 mL, 2.06 mmol) in MeCN (14 mL) at reflux for 16 h. Additional $K_2CO_3$ (0.15 g, 1.12 mmol) and 5-bromopent-1-ene (0.10 mL, 0.84 mmol) and stirred at 85 °C for 21 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (1.05 g). LCMS (Method 22): 2.26 min, 454.2 $[M-Boc+H]^+$.

**Intermediate 497:** Ethyl (*S*)-3-amino-3-(5-cyclopropyl-4-fluoro-2',3',4'-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00655]** A suspension of **Intermediate 496** (1.05 g, 1.66 mmol) in 4 M HCl in 1,4-dioxane (4.2 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (1.12 g). LCMS (Method 11): 2.58 min, 452.3 $[M-H]^-$.

**Intermediate 498:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2',3',4'-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00656]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 497** (1.12 g, 1.66 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.29 g, 2.45 mmol, CAS 413622-10-3), DIPEA (1.15 mL, 6.63 mmol), HOBt (0.25 g, 1.82 mmol) and EDCI (0.48 g, 2.49 mmol) in MeCN (16 mL) at RT for 16 h. Purified by flash chromatography (25 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.52 g). LCMS (Method 12): 1.95 min, 550.6 $[M-H]^-$.

**Intermediate 499:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2',3',4'-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00657]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 498** (0.52 g, 0.81 mmol), triethylamine (0.23 mL, 1.62 mmol) and methanesulfonyl chloride (94 µL, 1.21 mmol) in DCM (5 mL) at 0 °C for 10 min, then RT for 4 h to provide the title compound (0.55 g). LCMS (Method 15): 2.13 min, 628.3 $[M-H]^-$.

**Intermediate 500:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2',3',4'-trimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00658]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 499** (0.55 g, 0.69 mmol), **Intermediate 258** (0.19 g, 0.83 mmol) and $K_2CO_3$ (0.29 g, 2.07 mmol) in MeCN (9 mL) at reflux for 18 h. Purified by flash chromatography (25 g silica gel, 0-6% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.24 g). LCMS (Method 22): 2.25 min, 768.3 $[M+H]^+$.

**Intermediate 501:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^5$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00659]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 500** (0.24 g, 0.30 mmol) in DCE (0.14 L) and Grubbs II (26 mg, 30 µmol) at 50 °C for 3.5 h. Additional Grubbs II (13 mg, 15 µmol) was added and stirred at 50 °C for 1 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.16 g). LCMS (Method 15): 2.75 min, 740.3 $[M+H]^+$; olefin isomerisation metathesis product 2.70 min, 726.3 $[M-14+H]^+$.

**Intermediate 502:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^5$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00660]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 501** (0.16 g, 0.16 mmol) and 10% palladium on carbon (23 mg) in ethanol (16 mL) under a hydrogen

atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.12 g). LCMS (Method 15): 2.80 min, 742.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.74 min, 728.3 $[M-14+H]^+$.

**Intermediate 503**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4,4'-difluoro-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00661]** Prepared in an analogous manner to **Intermediate 3** using 2-bromo-5-fluoro-3-methylphenol (1.29 g, 6.28 mmol, CAS 1807192-21-7), **Intermediate 377** (2.50 g, 5.24 mmol), $K_3PO_4$ (3.34 g, 15.7 mmol), palladium acetate (0.12 g, 0.52 mmol) and tricyclohexyl phosphine (0.15 g, 0.52 mmol) in toluene (50 mL) and water (10 mL) at 100 °C for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (1.72 g). LCMS (Method 15): 2.42 min, 474.2 $[M-H]^-$.

**Intermediate 504:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4,4'-difluoro-2'-methyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00662]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 503** (2.00 g, 3.93 mmol), phenyl triflimide (1.41 g, 3.95 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (1.58 g, 4.81 mmol) in DCM (25 mL) at RT for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0–40% EtOAc in petroleum ether) to provide the title compound (2.56 g). LCMS (Method 11): 2.61 min, 608.2 $[M+H]^+$.

**Intermediate 505:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00663]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 504** (2.56 g, 3.79 mmol), 5-hexenylboronic acid (0.73 g, 5.69 mmol, CAS 1072952-16-9), $K_2CO_3$ (1.57 g, 11.4 mmol), palladium acetate (85 mg, 0.38 mmol) and RuPhos (0.27 g, 0.57 mmol) in toluene (80 mL) and water (15 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (1.97 g). LCMS (Method 15): 2.10 min, 442.2 $[M-Boc+H]^+$.

**Intermediate 506:** Ethyl (*S*)-3-amino-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00664]** A suspension of **Intermediate 505** (2.12 g, 3.64 mmol) in 4 M HCl in 1,4-dioxane (9.1 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (1.76 g). LCMS (Method 11): 2.74 min, 442.2 $[M+H]^+$.

**Intermediate 507:** Ethyl (*S*)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00665]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 506** (1.76 g, 3.23 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.56 g, 4.85 mmol, CAS 413622-10-3), DIPEA (1.73 mL, 9.69 mmol), HOBt (0.44 g, 3.23 mmol) and EDCI (0.74 g, 3.88 mmol) in MeCN (22 mL) at RT for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (1.53 g). LCMS (Method 22): 2.10 min, 540.2 $[M+H]^+$.

**Intermediate 508:** Ethyl (*S*)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00666]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 507** (1.0 g, 1.85 mmol), triethylamine (0.52 mL, 3.71 mmol) and methanesulfonyl chloride (0.17 mL, 2.24 mmol) in DCM (20 mL) at 0 °C for 10 min, then RT for 4 h to provide the title compound (1.24 g). LCMS (Method 12): 2.87 min, 616.5 $[M-H]^-$.

**Intermediate 509:** Ethyl (*S*)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00667]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 508** (0.62 g, 0.93 mmol), **Intermediate 258** (0.33 g, 1.40 mmol) and $K_2CO_3$ (0.39 g, 2.79 mmol) in MeCN (10 mL) at reflux for 18 h. Purified by reverse phase chromatography (105 g C18, 40-80% MeCN in 0.1% aqueous formic acid) to provide the title compound (0.23 g). LCMS (Method 15): 2.81 min, 754.6 $[M-H]^-$.

**Intermediate 510:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00668]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 509** (0.23 g, 0.30 mmol) in DCE (0.10 L) and Grubbs II (25 mg, 30 µmol) at 50 °C for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-7.5% MeOH in DCM) to provide the title compound (0.18 g). LCMS (Method 15): 2.80 min, 728.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.70 min, 714.2 $[M-14+H]^+$.

**Intermediate 511:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00669]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 510** (0.18 g, 0.25 mmol) and 10% palladium on carbon (26 mg) in ethanol (15 mL) under a hydrogen atmosphere at RT for 2 h. Additional 10% palladium on carbon (26 mg) was added and stirred

under a hydrogen atmosphere at RT for 0.5 h, to provide the title compound (0.18 g). LCMS (Method 15): 2.83 min, 730.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.73 min, 716.3 $[M-14+H]^+$.

**Intermediate 512**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-2'-hydroxy-6'-methyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00670]** Prepared in an analogous manner to **Intermediate 3** using 2-iodo-3-methyl-5-(trifluoromethyl)phenol (0.52 g, 1.54 mmol, CAS 2055497-48-6), **Intermediate 377** (0.97 g, 1.10 mmol), $K_3PO_4$ (0.66 g, 2.0 mmol), palladium acetate (35 mg, 0.16 mmol) and tricyclohexyl phosphine (43 mg, 0.15 mmol) in toluene (13.5 mL) and water (1.5 mL) at 100 °C for 20 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.53 g). LCMS (Method 12): 1.83 min, 524.5 $[M-H]^-$.

**Intermediate 513:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00671]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 512** (0.53 g, 0.96 mmol), $K_2CO_3$ (0.20 g, 1.45 mmol) and 5-bromopent-1-ene (0.20 mL, 1.69 mmol) in MeCN (5 mL) at reflux for 21 h. Purified by flash chromatography (25 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.79 g). LCMS (Method 12): 2.10 min, 495.4 $[M-Boc+H]^+$.

**Intermediate 514:** Ethyl (*S*)-3-amino-3-(5-cyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00672]** A suspension of **Intermediate 513** (0.79 g, 1.33 mmol) in 4 M HCl in 1,4-dioxane (3 mL) was stirred at RT for 18 h. The mixture was concentrated under reduced pressure to provide the title compound (0.47 g). LCMS (Method 19): 5.57 min, 495.4 $[M+H]^+$.

**Intermediate 515:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00673]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 514** (0.47 g, 0.82 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.10 g, 0.89 mmol, CAS 413622-10-3), DIPEA (0.50 mL, 2.81 mmol), HOBt (0.12 g, 0.89 mmol) and EDCI (0.21 g, 1.07 mmol) in MeCN (10 mL) at RT for 19 h. Purified by flash chromatography (12 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.35 g). LCMS (Method 12): 1.99 min, 590.5 $[M-H]^-$.

**Intermediate 516:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00674]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 515** (0.35 g, 0.56 mmol), triethylamine (0.16 mL, 1.15 mmol) and methanesulfonyl chloride (0.07 mL, 0.90 mmol) in DCM (6 mL) at 0 °C for 10 min, then RT for 1 h to provide the title compound (0.43 g). LCMS (Method 12): 2.27 min, 668.5 $[M-H]^-$.

**Intermediate 517:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-methyl-6'-(pent-4-en-1-yloxy)-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00675]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 516** (0.44 g, 0.56 mmol), **Intermediate 258** (0.13 g, 0.56 mmol) and $K_2CO_3$ (0.23 g, 1.67 mmol) in MeCN (6 mL) at reflux for 24 h. Purified by reverse phase chromatography (105 g C18, 40-80% MeCN in 0.1% aqueous formic acid) to provide the title compound (0.15 g). LCMS (Method 21): 6.26 min, 808.2 $[M+H]^+$.

**Intermediate 518:** Ethyl 2-((10*S*,13*S*)-1$^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-11-oxo-2$^4$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00676]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 517** (0.15 g, 0.17 mmol) in DCE (85 mL) and Grubbs II (16 mg, 19 µmol) at 50 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.10 g). LCMS (Method 21): 5.70 min, 780.3 $[M+H]^+$; olefin isomerisation metathesis product: 5.58 min, 766.2 $[M-14+H]^+$.

**Intermediate 519:** Ethyl 2-((10*S*,13*S*)-1$^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-11-oxo-2$^4$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00677]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 518** (0.10 g, 0.08 mmol) and 10% palladium on carbon (17 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 4.5 h. Additional 10% palladium on carbon (17 mg) was added and stirred under a hydrogen atmosphere at RT for 2 h, to provide the title compound (86 mg). LCMS (Method 21): 5.80 min, 782.3 $[M+H]^+$; olefin isomerisation metathesis product: 5.68 min, 768.2 $[M-14+H]^+$.

**Intermediate 520:** Ethyl (*S*)-3-amino-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00678]** A suspension of **Intermediate 415** (2.16 g, 3.62 mmol) in 4 M HCl in 1,4-dioxane (9 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (1.80 g). LCMS (Method 22): 2.18 min, 466.1 $[M+H]^+$.

**Intermediate 521:** Ethyl (*S*)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00679]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 520** (1.80 g, 3.59 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.62 g, 5.38 mmol, CAS 413622-10-3), DIPEA (1.87 mL, 10.8 mmol), HOBt (0.48 g, 3.59 mmol) and EDCI (0.82 g, 4.30 mmol) in MeCN (25 mL) at RT for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (1.59 g). LCMS (Method 15): 2.76 min, 564.2 $[M+H]^+$.

**Intermediate 522:** Ethyl (*S*)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00680]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 521** (0.75 g, 1.22 mmol), triethylamine (0.34 mL, 2.45 mmol) and methanesulfonyl chloride (0.14 mL, 1.84 mmol) in DCM (9 mL) at 0 °C for 10 min, then RT for 1.5 h to provide the title compound (0.84 g). LCMS (Method 15): 2.81 min, 640.2 $[M-H]^-$.

**Intermediate 523:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00681]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 522** (0.84 g, 1.44 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.35 g, 1.44 mmol, CAS 109919-32-6) and $K_2CO_3$ (0.46 g, 3.32 mmol) in MeCN (17 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.84 g). LCMS (Method 15): 2.98 min, 789.1 $[M+H]^+$.

**Intermediate 524:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00682]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 523** (0.77 g, 0.97 mmol) in DCE (0.40 L) and Grubbs II (83 mg, 97 µmol) at 45 °C for 2 h, with nitrogen bubbled through the reaction mix. Purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.58 g). LCMS (Method 15): 2.90 min, 761.1 $[M+H]^+$.

**Intermediate 525:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00683]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 524** (0.26 g, 0.34 mmol) and 10% palladium on carbon (36 mg) in EtOAc (26 mL) under a hydrogen atmosphere at RT for 1.5 h, to provide the title compound (0.25 g). LCMS (Method 15): 2.92 min, 763.1 $[M+H]^+$.

**Intermediate 526:** Ethyl 2-((3*S*,6*S*)-6-(5-((*E*)-2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00684]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 525** (0.25 g, 0.33 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (65 mg, 0.33 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (24 mg, 0.03 mmol) and $Na_2CO_3$ (69 mg, 0.65 mmol) in 1,4-dioxane (9 mL) and water (3 mL) at 90 °C for 1.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.16 g). LCMS (Method 22): 2.95 min, 753.2 $[M+H]^+$.

**Intermediate 527:** Ethyl 2-((3*S*,6*S*)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-6-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00685]** A solution of **Intermediate 526** (0.16 g, 0.21 mmol) in DCM (11 mL) and TFA (1.1 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.23 g). LCMS (Method 22): 2.76 min, 725.2 $[M+H]^+$.

**Intermediate 528:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00686]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 527** (0.16 g, 0.21 mmol), azetidine (17 µL, 0.26 mmol), triethylamine (0.24 mL, 1.71 mmol) in DCM (1.5 mL) and 4 Å molecular sieves at RT for 3 h, then STAB (91 mg, 0.43 mmol) at RT for 18 h. purified by catch and release chromatography (1 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (79 mg). LCMS (Method 22): 2.94 min, 766.3 $[M+H]^+$.

**Intermediate 529:** 5-(2-(3-Fluoroazetidin-1-yl)ethyl)-2-methoxy-4-(trifluoromethyl)pyridine

**[00687]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 322** (1.18 g, 5.39 mmol), 3-fluoroazetidine hydrochloride (0.72 g, 6.47 mmol, CAS 617718-46-4),

triethylamine (1.50 mL, 10.8 mmol) in DCM (18 mL) and 4 Å molecular sieves at RT for 4 h, then STAB (2.28 g, 10.8 mmol) at RT for 16 h, to provide the title compound (1.27 g). LCMS (Method 22): 1.55 min, 279.0 $[M+H]^+$.

**Intermediate 530:** 5-(2-((3-Bromo-2-fluoropropyl)amino)ethyl)-4-(trifluoromethyl)pyridin-2-ol

**[00688]** A solution of **Intermediate 529** (1.1 g, 3.95 mmol) in 33% HBr in AcOH (6.83 mL, 39.5 mmol) was stirred at 85 °C for 2 h. The mixture was cooled and concentrated under reduced pressure. The crude product was purified by catch and release chromatography (20 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (1.7 g). LCMS (Method 15): 1.13 min, 344.9 $[M+H]^+$.

**Intermediate 531:** 5-(2-(3-Fluoroazetidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-2-ol

**[00689]** A suspension of **Intermediate 530** (1.06 g, 3.07 mmol) and sodium hydroxide (2 M aqueous, 6.14 mL) in MeCN (16 mL) was stirred at 50 °C for 4 h. The mixture was concentrated under reduced pressure and purified by reverse-phase chromatography (55 g C18, eluting 5-35% MeCN in 0.1% aqueous ammonia) to provide the title compound (0.37 g). $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.72 (s, 1H), 6.61 (s, 1H), 5.23 – 5.01 (m, 1H), 3.70 – 3.60 (m, 2H), 3.26 (ddd, 2H), 2.70 – 2.62 (m, 2H), 2.64 – 2.56 (m, 2H).

**Intermediate 532:** Ethyl (*S*)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00690]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 508** (0.62 g, 0.93 mmol), **Intermediate 531** (0.37 g, 1.40 mmol) and $K_2CO_3$ (0.39 g, 2.79 mmol) in MeCN (10 mL) at reflux for 18 h. Purified by reverse phase chromatography (32 g C18, 40-80% MeCN in 0.1% aqueous formic acid) to provide the title compound (0.21 g). LCMS (Method 15): 2.85 min, 786.3 $[M+H]^+$.

**Intermediate 533:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00691]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 532** (0.21 g, 0.27 mmol) in DCE (0.11 L) and Grubbs II (23 mg, 27 µmol) at 50 °C for 1 h. Purified by flash chromatography (24 g silica gel, eluting 0-4% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.22 g). LCMS (Method 15): 2.14 min, 758.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.08 min, 744.3 $[M-14+H]^+$.

**Intermediate 534:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00692]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 533** (0.22 g, 0.21 mmol) and 10% palladium on carbon (34 mg) in ethanol (7 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-4% (0.5% ammonia MeOH) in DCM) to provide the title compound (86 mg). LCMS (Method 15): 2.16 min, 760.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.09 min, 746.3 $[M-14+H]^+$.

**Intermediate 535:** Ethyl (*S*)-3-(4'-bromo-4-fluoro-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00693]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 223** (2.0 g, 4.57 mmol), **Intermediate 336** (1.57 g, 5.03 mmol), $Na_2CO_3$ (1.45 g, 13.7 mmol) and Pd(dppf)$Cl_2$ (0.37 g, 0.46 mmol) in 1,4-dioxane (40 mL), and water (4 mL) at 85 °C for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (1.26 g). LCMS (Method 22): 1.86 min, 494.1 $[M-H]^-$.

**Intermediate 536:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-cyclopropyl-4-fluoro-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00694]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 535** (1.66 g, 3.33 mmol), cyclopropaneboronic acid (0.34 g, 4.00 mmol), $K_3PO_4$ (2.12 g, 10.0 mmol), palladium acetate (75 mg, 0.33 mmol) and tricyclohexyl phosphine (94 mg, 0.33 mmol) in toluene (33 mL) and water (6.6 mL) at 110 °C for 18 h. Purified by flash chromatography (20 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.83 g). LCMS (Method 22): 1.88 min, 358.1 $[M-Boc+H]^+$.

**Intermediate 537:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-cyclopropyl-4-fluoro-2'-methyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00695]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 536** (1.06 g, 2.32 mmol), phenyl triflimide (0.83 g, 2.32 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (0.91 g, 2.78 mmol) in DCM (17 mL) at RT for 16 h. Purified by flash chromatography (24 g silica gel, eluting 0–20% EtOAc in petroleum ether) to provide the title compound (0.96 g). LCMS (Method 22): 2.10 min, 588.2 $[M-H]^-$.

**Intermediate 538:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00696]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 537** (0.96 g, 1.63 mmol), 5-hexenylboronic acid (0.31 g, 2.44 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.68

g, 4.89 mmol), palladium acetate (37 mg, 0.16 mmol) and RuPhos (0.11 g, 0.24 mmol) in toluene (32 mL) and water (8 mL) at 110 °C for 18 h. Purified by flash chromatography (24 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.81 g). LCMS (Method 22): 2.27 min, 424.2 $[M\text{-}Boc+H]^+$.

**Intermediate 539:** Ethyl (*S*)-3-(4'-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00697]** A suspension of **Intermediate 538** (0.81 g, 1.46 mmol) in 4 M HCl in 1,4-dioxane (7.3 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure. This was suspended in MeCN (15 mL) and (2*R*)-2-hydroxypent-4-enoic acid (0.24 g, 2.06 mmol, CAS 413622-10-3), DIPEA (0.96 mL, 5.50 mmol), HOBt (0.20 g, 1.51 mmol) and EDCI (0.40 g, 2.06 mmol) were added and the mixture was stirred at RT for 18 h. The mixture was diluted with water and extracted into EtOAc. The organic layer was washed with brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (24 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.60 g). LCMS (Method 22): 2.10 min, 522.2 $[M+H]^+$.

**Intermediate 540:** Ethyl (*S*)-3-(4'-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00698]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 539** (0.60 g, 1.14 mmol), triethylamine (0.32 mL, 2.29 mmol) and methanesulfonyl chloride (0.13 mL, 1.71 mmol) in DCM (21 mL) at 0 °C for 10 min, then RT for 2 h to provide the title compound (0.63 g). LCMS (Method 22): 2.13 min, 600.2 $[M+H]^+$.

**Intermediate 541:** Ethyl (*S*)-3-(4'-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00699]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 540** (0.63 g, 0.94 mmol), **Intermediate 258** (0.26 g, 1.13 mmol) and $K_2CO_3$ (0.39 g, 2.82 mmol) in MeCN (15 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica gel, 0-8% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.29 g). LCMS (Method 15): 2.91 min, 738.3 $[M+H]^+$.

**Intermediate 542:** Ethyl 2-((3*S*,6*S*)-$1^4$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00700]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 541** (0.29 g, 0.39 mmol) in DCE (0.21 L) and Grubbs II (33 mg, 39 µmol) at 50 °C for 3 h. Purified by

flash chromatography (12 g silica gel, eluting 0-6% MeOH in DCM) to provide the title compound (0.33 g). LCMS (Method 15): 2.81 min, 710.2 $[M+H]^+$; olefin isomerisation metathesis product: 2.71 min, 696.2 $[M-14+H]^+$.

**Intermediate 543:** Ethyl 2-((3*S*,6*S*)-$1^4$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00701]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 542** (0.33 g, 0.28 mmol) and 10% palladium on carbon (29 mg) in ethanol (32 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.24 g). LCMS (Method 15): 2.83 min, 712.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.73 min, 698.3 $[M-14+H]^+$.

**Intermediate 544:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2'-hydroxy-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00702]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 223** (1.44 g, 3.13 mmol), 2-bromo-3,5-dimethyl-phenol (0.94 g, 4.69 mmol, CAS 125237-08-3), $K_3PO_4$ (1.33 g, 6.26 mmol), palladium acetate (70 mg, 0.31 mmol) and tricyclohexyl phosphine (88 mg, 0.31 mmol) in toluene (28 mL) and water (3.5 mL) at 100 °C for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (1.48 g). LCMS (Method 22): 1.82 min, 430.2 $[M-H]^-$.

**Intermediate 545:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2',4'-dimethyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00703]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 544** (1.48 g, 2.81 mmol), phenyl triflimide (1.01 g, 2.81 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (1.10 g, 3.38 mmol) in DCM (19 mL) at RT for 16 h. Purified by flash chromatography (24 g silica gel, eluting 0–30% EtOAc in petroleum ether) to provide the title compound (1.56 g). LCMS (Method 22): 2.06 min, 562.1 $[M-H]^-$.

**Intermediate 546:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00704]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 545** (1.56 g, 2.55 mmol), 5-hexenylboronic acid (0.49 g, 3.82 mmol, CAS 1072952-16-9), $K_2CO_3$ (1.06 g, 7.64 mmol), palladium acetate (57 mg, 0.26 mmol) and RuPhos (0.18 g, 0.38 mmol) in toluene (51 mL) and water (6 mL) at 100 °C for 18 h. Purified by flash chromatography (24 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.97 g). LCMS (Method 22): 2.25 min, 398.1 $[M-Boc+H]^+$.

**Intermediate 547:** Ethyl (*S*)-3-amino-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00705]** A suspension of **Intermediate 546** (0.97 g, 1.85 mmol) in 4 M HCl in 1,4-dioxane (4.6 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure to provide the title compound (1.07 g). LCMS (Method 22): 2.11 min, 398.1 $[M+H]^+$.

**Intermediate 548:** Ethyl (*S*)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00706]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 547** (1.07 g, 1.90 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.33 g, 2.85 mmol, CAS 413622-10-3), DIPEA (1.32 mL, 7.59 mmol), HOBt (0.28 g, 2.09 mmol) and EDCI (0.55 g, 2.85 mmol) in MeCN (17 mL) at RT for 20 h. Purified by flash chromatography (25 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.70 g). LCMS (Method 22): 2.07 min, 496.2 $[M+H]^+$.

**Intermediate 549:** Ethyl (*S*)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00707]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 548** (0.70 g, 1.28 mmol), triethylamine (0.36 mL, 2.56 mmol) and methanesulfonyl chloride (0.15 mL, 1.92 mmol) in DCM (13 mL) at 0 °C for 10 min, then RT for 1.5 h to provide the title compound (0.73 g). LCMS (Method 22): 2.10 min, 574.2 $[M+H]^+$.

**Intermediate 550:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00708]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 549** (0.73 g, 1.28 mmol), **Intermediate 258** (0.36 g, 1.54 mmol) and $K_2CO_3$ (0.53 g, 3.84 mmol) in MeCN (13 mL) at reflux for 24 h. Purified by flash chromatography (25 g silica gel, 0-6% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.33 g). LCMS (Method 22): 2.22 min, 712.3 $[M+H]^+$.

**Intermediate 551:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00709]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 550** (0.33 g, 0.47 mmol) in DCE (0.20 L) and Grubbs II (40 mg, 47 µmol) at 50 °C for 3 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title

compound (0.33 g). LCMS (Method 15): 2.76 min, 684.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.65 min, 670.3 $[M-14+H]^+$.

**Intermediate 552:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00710]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 551** (0.38 g, 0.56 mmol) and 10% palladium on carbon (59 mg) in ethanol (6 mL) under a hydrogen atmosphere at RT for 3.5 h. Purified by flash chromatography (4 g silica gel, eluting 0-4% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.27 g). LCMS (Method 15): 2.81 min, 686.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.70 min, 672.3 $[M-14+H]^+$.

**Intermediate 553:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00711]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 436** (0.42 g, 0.62 mmol), **Intermediate 137** (0.12 g, 0.74 mmol) and $K_2CO_3$ (0.26 g, 1.85 mmol) in MeCN (10 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica, eluting 0-6% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.16 g). LCMS (Method 15): 2.85 min, 684.3 $[M+H]^+$.

**Intermediate 554:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00712]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 553** (0.16 g, 0.23 mmol) in DCE (0.11 L) and Grubbs II (19 mg, 23 μmol) at 50 °C for 4 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.15 g). LCMS (Method 15): 2.75 min, 656.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.65 min, 642.3 $[M-14+H]^+$.

**Intermediate 555:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00713]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 554** (0.15 g, 0.18 mmol) and 10% palladium on carbon (25 mg) in ethanol (12 mL) under a hydrogen atmosphere at RT for 5 h. Conditions repeated. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (99 mg). LCMS (Method 15): 2.75 min, 658.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.65 min, 644.3 $[M-14+H]^+$.

**Intermediate 556:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2',4',5-trimethyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00714]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 283** (0.81 g, 1.61 mmol), phenyl triflimide (0.57 g, 1.61 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (0.63 g, 1.93 mmol) in DCM (11 mL) at RT for 16 h. Purified by flash chromatography (25 g silica gel, eluting 0–30% EtOAc in petroleum ether) to provide the title compound (0.80 g). LCMS (Method 22): 2.12 min, 576.1 $[M-H]^-$.

**Intermediate 557:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00715]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 556** (0.80 g, 1.28 mmol), 5-hexenylboronic acid (0.25 g, 1.92 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.53 g, 3.84 mmol), palladium acetate (29 mg, 0.13 mmol) and RuPhos (90 mg, 0.19 mmol) in toluene (26 mL) and water (3 mL) at 100 °C for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.61 g). LCMS (Method 22): 2.30 min, 510.3 $[M-H]^-$.

**Intermediate 558:** Ethyl (*S*)-3-amino-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00716]** A suspension of **Intermediate 557** (0.61 g, 1.11 mmol) in 4 M HCl in 1,4-dioxane (2.8 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (0.55 g). LCMS (Method 12): 2.09 min, 412.6 $[M+H]^+$.

**Intermediate 559:** Ethyl (*S*)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00717]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 558** (0.55 g, 1.01 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.18 g, 1.51 mmol, CAS 413622-10-3), DIPEA (0.70 mL, 4.04 mmol), HOBt (0.15 g, 1.11 mmol) and EDCI (0.29 g, 1.51 mmol) in MeCN (9 mL) at RT for 20 h. Purified by flash chromatography (12 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.43 g). LCMS (Method 22): 2.12 min, 510.2 $[M+H]^+$.

**Intermediate 560:** Ethyl (*S*)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00718]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 559** (0.43 g, 0.79 mmol), triethylamine (0.22 mL, 1.58 mmol) and methanesulfonyl chloride (92 µL, 1.18 mmol) in DCM (8 mL) at 0 °C for 10 min, then RT for 3 h. Additional methanesulfonyl chloride

(46 µL, 0.59 mmol) added and stirred at RT for 18 h, to provide the title compound (0.49 g). LCMS (Method 22): 2.77 min, 588.3 $[M+H]^+$.

**Intermediate 561:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00719]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 560** (0.49 g, 0.71 mmol), **Intermediate 258** (0.20 g, 0.85 mmol) and $K_2CO_3$ (0.29 g, 2.13 mmol) in MeCN (11 mL) at reflux for 24 h. Purified by flash chromatography (40 g silica gel, 0-3% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.22 g). LCMS (Method 15): 2.93 min, 726.3 $[M+H]^+$.

**Intermediate 562:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$,2$^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00720]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 561** (0.22 g, 0.29 mmol) in DCE (0.14 L) and Grubbs II (25 mg, 29 µmol) at 50 °C for 4 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.19 g). LCMS (Method 11): 2.76 min, 696.6 $[M-H]^-$; olefin isomerisation metathesis product: 2.64 min, 682.6 $[M-14-H]^-$.

**Intermediate 563:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$,2$^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00721]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 562** (0.19 g, 0.27 mmol) and 10% palladium on carbon (29 mg) in ethanol (14 mL) under a hydrogen atmosphere at RT for 4 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.13 g). LCMS (Method 15): 2.87 min, 700.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.76 min, 686.3 $[M-14+H]^+$.

**Intermediate 564:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4-fluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00722]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 351** (1.10 g, 1.71 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.50 g, 2.05 mmol, CAS 109919-32-6) and $K_2CO_3$ (0.71 g, 5.13 mmol) in MeCN (14 mL) at reflux for 16 h. Purified by flash chromatography (80 g silica gel, eluting 0-80% EtOAc -in petroleum ether) to provide the title compound (0.73 g). LCMS (Method 15): 2.88 min, 791.1 $[M+H]^+$.

**Intermediate 565:** Ethyl 2-((10*S*,13*S*)-10-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00723]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 564** (0.73 g, 0.93 mmol) in DCE (0.31 L) and Grubbs II (58 mg, 69 µmol) at 50 °C for 1.5 h. Purified by flash chromatography (40 g silica gel, eluting 10-60% EtOAc in petroleum ether) to provide the title compound (0.62 g). LCMS (Method 15): 2.77 min, 761.1 $[M+H]^+$.

**Intermediate 566:** Ethyl 2-((10*S*,13*S*)-10-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00724]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 565** (0.68 g, 0.89 mmol) and 10% palladium on carbon (94 mg) in EtOAc (60 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (40 g silica gel, eluting 5-100% EtOAc in petroleum ether) to provide the title compound (0.73 g). LCMS (Method 15): 2.80 min, 765.1 $[M+H]^+$.

**Intermediate 567:** Ethyl 2-((10*S*,13*S*)-10-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00725]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 566** (0.27 g, 0.35 mmol), $Pd(PPh_3)_2Cl_2$ (25 mg, 35 µmol), copper(I) iodide (6.7 mg, 35 µmol), triethylamine (0.49 mL, 3.54 mmol) and *N*,*N*-dimethylpropargylamine (0.38 mL, 3.54 mmol, CAS 7223-38-3) in MeCN (5.6 mL) at 80 °C for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-100% EtOAc in petroleum ether), to provide the title compound (0.21 g). LCMS (Method 11): 2.62 min, 767.7 $[M+H]^+$.

**Intermediate 568:** Ethyl 2-((10*S*,13*S*)-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00726]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 567** (0.21 g, 0.27 mmol) and 10% palladium on carbon (29 mg) in ethanol (22 mL) under a hydrogen atmosphere at RT for 16 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.18 g). LCMS (Method 21): 2.80 min, 770.3 $[M+H]^+$.

**Intermediate 569:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00727]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 436** (0.36 g, 0.59 mmol), **Intermediate 531** (0.23 g, 0.88 mmol) and $K_2CO_3$ (0.24 g, 1.76 mmol) in MeCN (5 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica, eluting 10-100% EtOAc in petroleum ether) to provide the title compound (0.19 g). LCMS (Method 15): 2.93 min, 782.3 $[M+H]^+$.

**Intermediate 570:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$2^4$-fluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00728]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 569** (0.18 g, 0.17 mmol) in DCE (76 mL) and Grubbs II (11 mg, 12 µmol) at 50 °C for 1.5 h. Purified by flash chromatography (40 g silica gel, eluting 10-100% EtOAc in petroleum ether then 10% MeOH in DCM) to provide the title compound (0.14 g). LCMS (Method 11): 2.73 min, 752.7 $[M-H]^-$.

**Intermediate 571:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$2^4$-fluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00729]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 570** (0.13 g, 0.17 mmol) and 10% palladium on carbon (18 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.12 g). LCMS (Method 15): 2.87 min, 756.3 $[M+H]^+$.

**Intermediate 572:** Ethyl 2-((10*S*,13*S*)-10-(5-((*E*)-2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-$1^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00730]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 566** (0.43 g, 0.56 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (0.11 g, 0.56 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (41 mg, 0.06 mmol) and $Na_2CO_3$ (0.12 g, 1.13 mmol) in 1,4-dioxane (21 mL) and water (7 mL) at 95 °C for 1.5 h. Purified by flash chromatography (40 g silica gel, eluting 0-70% EtOAc in petroleum ether) to provide the title compound (0.30 g). LCMS (Method 27): 2.55 min, 755.2 $[M+H]^+$.

**Intermediate 573:** Ethyl 2-((10*S*,13*S*)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-10-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00731]** A solution of **Intermediate 572** (0.20 g, 0.27 mmol) in DCM (14 mL) and TFA (1.3 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.15 g). LCMS (Method 15): 2.62 min, 727.2 $[M+H]^+$.

**Intermediate 574:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-$1^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00732]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 573** (0.15 g, 0.14 mmol), azetidine (11 µL, 0.17 mmol), triethylamine (0.15 mL, 1.11 mmol) in DCM (3 mL) and 4 Å molecular sieves at RT for 4 h, then STAB (59 mg, 0.28 mmol) at RT for 16 h. Purified by reverse phase chromatography (38 g C18, eluting 5-90% MeCN in 0.1% aqueous ammonia) to provide the title compound (68 mg). LCMS (Method 11): 2.77 min, 768.0 $[M+H]^+$.

**Intermediate 575:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00733]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 525** (0.24 g, 0.31 mmol), $Pd(PPh_3)_2Cl_2$ (22 mg, 31 µmol), copper(I) iodide (6.0 mg, 31 µmol), triethylamine (0.44 mL, 3.13 mmol) and *N*,*N*-dimethylpropargylamine (0.34 mL, 3.13 mmol, CAS 7223-38-3) in MeCN (5 mL) at 65 °C for 18 h. Additional triethylamine (0.22 mL, 1.56 mmol) and *N*,*N*-dimethylpropargylamine (0.17 mL, 1.56 mmol) were added and stirred at 65 °C for 24 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM) and catch and release chromatography (1 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH), to provide the title compound (0.10 g). LCMS (Method 15): 2.87 min, 764.3 $[M+H]^+$.

**Intermediate 576:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00734]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 575** (0.10 g, 0.13 mmol) and 10% palladium on carbon (14 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-5% (0.5% ammonia MeOH) in DCM) to provide the title compound (74 mg). LCMS (Method 15): 2.99 min, 768.3 $[M+H]^+$.

**Intermediate 577:** Ethyl 2-((10*S*,13*S*)-10-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$-cyclopropyl-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00735]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 425** (0.25 g, 0.34 mmol) and 10% palladium on carbon (36 mg) in EtOAc (25 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (40 g silica gel, eluting 5-100% EtOAc in petroleum ether) to provide the title compound (0.18 g). LCMS (Method 15): 2.82 min, 735.1 $[M+H]^+$.

**Intermediate 578:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-((*E*)-2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00736]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 577** (0.18 g, 0.25 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (54 mg, 0.27 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (18 mg, 25 μmol) and $Na_2CO_3$ (52 mg, 0.50 mmol) in 1,4-dioxane (9 mL) and water (3 mL) at 90 °C for 1 h. Purified by flash chromatography (4 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.12 g). LCMS (Method 15): 2.84 min, 727.3 $[M+H]^+$.

**Intermediate 579:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-10-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00737]** A solution of **Intermediate 578** (0.14 g, 0.19 mmol) in DCM (9 mL) and TFA (0.9 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.13 g). LCMS (Method 22): 2.61 min, 699.3 $[M+H]^+$.

**Intermediate 580:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$-cyclopropyl-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00738]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 579** (0.13 g, 0.19 mmol), azetidine (15 μL, 0.22 mmol), triethylamine (0.10 mL, 0.75 mmol) in DCM (1.5 mL) and 4 Å molecular sieves at RT for 3 h, then STAB (79 mg, 0.28 mmol) at RT for 40 h. Purified by catch and release chromatography (1 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (89 mg). LCMS (Method 15): 2.73 min, 740.3 $[M+H]^+$.

**Intermediate 581:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00739]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 468** (0.30 g, 0.41 mmol) and 10% palladium on carbon (44 mg) in EtOAc (30 mL) under a hydrogen

atmosphere at RT for 1 h. Purified by flash chromatography (12 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.29 g). LCMS (Method 15): 2.96 min, 735.1 $[M+H]^+$.

**Intermediate 582:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-((*E*)-2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00740]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 581** (0.28 g, 0.36 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (79 mg, 0.40 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (27 mg, 36 µmol) and $Na_2CO_3$ (77 mg, 0.73 mmol) in 1,4-dioxane (12 mL) and water (4 mL) at 90 °C for 1 h. Purified by flash chromatography (12 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.21 g). LCMS (Method 15): 2.98 min, 725.3 $[M+H]^+$.

**Intermediate 583:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-6-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00741]** A solution of **Intermediate 582** (0.21 g, 0.25 mmol) in DCM (17 mL) and TFA (1.2 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.17 g). LCMS (Method 15): 2.79 min, 697.2 $[M+H]^+$.

**Intermediate 584:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00742]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 583** (0.17 g, 0.25 mmol), azetidine (20 µL, 0.30 mmol), triethylamine (0.29 mL, 1.98 mmol) in DCM (9 mL) and 4 Å molecular sieves at RT for 4.5 h, then STAB (0.11 g, 0.50 mmol) at RT for 16 h. Purified by catch and release chromatography (1 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (71 mg). LCMS (Method 15): 2.95 min, 738.3 $[M+H]^+$.

**Intermediate 585:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00743]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 508** (2.16 g, 2.97 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (1.08 g, 4.46 mmol, CAS 109919-32-6) and $K_2CO_3$ (1.23 g, 8.92 mmol) in MeCN (30 mL) at reflux for 24 h. Purified by flash

chromatography (120 g silica gel, 0-50% EtOAc in petroleum ether) to provide the title compound (1.41 g). LCMS (Method 15): 2.93 min, 765.1 $[M+H]^+$.

**Intermediate 586:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00744]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 585** (1.41 g, 1.75 mmol) in DCE (0.6 L) and Grubbs II (0.15 g, 0.18 mmol) at 50 °C for 3 h. Purified by flash chromatography (40 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (1.20 g). LCMS (Method 15): 2.80 min, 737.1 $[M+H]^+$.

**Intermediate 587:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00745]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 586** (1.20 g, 1.63 mmol) and 10% palladium on carbon (0.17 g) in EtOAc (0.12 L) under a hydrogen atmosphere at RT for 2 h. Purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.95 g). LCMS (Method 15): 2.89 min, 739.2 $[M+H]^+$.

**Intermediate 588:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-((*E*)-2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00746]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 587** (0.25 g, 0.34 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (74 mg, 0.37 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (25 mg, 34 µmol) and $Na_2CO_3$ (72 mg, 0.68 mmol) in 1,4-dioxane (12 mL) and water (4 mL) at 90 °C for 1.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.12 g). LCMS (Method 15): 2.91 min, 729.3 $[M+H]^+$.

**Intermediate 589:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-6-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00747]** A solution of **Intermediate 588** (0.12 g, 0.16 mmol) in DCM (7.6 mL) and TFA (0.78 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.11 g). LCMS (Method 15): 2.71 min, 701.2 $[M+H]^+$.

**Intermediate 590:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00748]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 589** (0.11 g, 0.16 mmol), azetidine (14 µL, 0.21 mmol), triethylamine (95 µL, 0.69 mmol) in DCM (1.7 mL) and 4 Å molecular sieves at RT for 2 h, then STAB (73 mg, 0.34 mmol) at RT for 18 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (71 mg). LCMS (Method 15): 2.85 min, 742.3 $[M+H]^+$.

**Intermediate 591:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00749]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 436** (0.61 g, 1.0 mmol), 5-bromo-3-fluoropyridin-2-ol (0.21 g, 1.10 mmol, CAS 156772-63-3) and $K_2CO_3$ (0.41 g, 3.0 mmol) in MeCN (13 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica, eluting 0-10% MeOH in DCM) then reverse phase chromatography (55 g C18, eluting 60-100% MeCN in 0.1% aqueous formic acid) to provide the title compound (0.33 g). LCMS (Method 15): 2.92 min, 711.2 $[M+H]^+$.

**Intermediate 592:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00750]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 591** (0.33 g, 0.47 mmol) in DCE (0.22 L) and Grubbs II (40 mg, 47 µmol) at 50 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.42 g). LCMS (Method 15): 2.85 min, 683.1 $[M+H]^+$.

**Intermediate 593:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-2$^4$-fluoro-6-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00751]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 592** (0.27 g, 0.23 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (45 mg, 0.23 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (17 mg, 23 µmol) and $Na_2CO_3$ (48 mg, 0.46 mmol) in 1,4-dioxane (7.4 mL) and water (2.5 mL) at 85 °C for 1 h. Purified by flash chromatography (25 g silica gel, eluting 0-100% EtOAc in petroleum ether). The residue was dissolved in DCM (25 mL) and TFA (6.2 mL) and stirred at RT for 1 h, concentrated under reduced pressure, to provide the title compound (0.24 g). LCMS (Method 15): 2.69 min, 645.2 $[M+H]^+$.

**Intermediate 594:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00752]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 593** (0.26 g, 0.22 mmol), azetidine (18 µL, 0.26 mmol), triethylamine (92 µL, 0.66 mmol) in DCM (8 mL) and 4 Å molecular sieves at RT for 1.5 h, then STAB (93 mg, 0.44 mmol) at RT for 18 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (87 mg). LCMS (Method 15): 2.84 min, 686.3 $[M+H]^+$.

**Intermediate 595:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00753]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 594** (87 mg, 0.08 mmol) and 10% palladium on carbon (9 mg) in ethanol (5 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (40 g silica gel, eluting 5-10% MeOH in DCM) to provide the title compound (79 mg). LCMS (Method 15): 2.84 min, 688.3 $[M+H]^+$.

**Intermediate 596**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-2'-hydroxy-4'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00754]** Prepared in an analogous manner to **Intermediate 3** using 2-bromo-5-methylphenol (0.38 g, 2.03 mmol, CAS 14847-51-9), **Intermediate 377** (1.20 g, 2.01 mmol), $K_3PO_4$ (0.86 g, 4.05 mmol), palladium acetate (46 mg, 0.21 mmol) and tricyclohexyl phosphine (60 mg, 0.21 mmol) in toluene (10 mL) and water (1 mL) at 100 °C for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.75 g). LCMS (Method 22): 1.90 min, 456.3 $[M-H]^-$.

**Intermediate 597:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-4'-methyl-2'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00755]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 596** (0.75 g, 1.43 mmol), phenyl triflimide (0.55 g, 1.54 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (0.50 g, 1.54 mmol) in DCM (10 mL) at RT for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0–15% EtOAc in petroleum ether) to provide the title compound (0.78 g). LCMS (Method 12): 2.00 min, 588.4 $[M-H]^-$.

**Intermediate 598:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00756]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 597** (0.78 g, 1.29 mmol), 5-hexenylboronic acid (0.25 g, 1.95 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.54 g, 3.87 mmol), palladium acetate (30 mg, 0.13 mmol) and RuPhos (90 mg, 0.19 mmol) in toluene (10 mL) and water (2 mL) at reflux for 3 h. Purified by flash chromatography (15 g silica gel, eluting 0-10% EtOAc in petroleum ether) to provide the title compound (0.58 g). LCMS (Method 12): 2.19 min, 424.3 $[M\text{-Boc}+H]^+$.

**Intermediate 599:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00757]** A suspension of **Intermediate 598** (0.58 g, 1.09 mmol) in 4 M HCl in 1,4-dioxane (3 mL) was stirred at RT for 20 h. The mixture was concentrated under reduced pressure. This was suspended in MeCN (10 mL) and (2*R*)-2-hydroxypent-4-enoic acid (0.13 g, 1.13 mmol, CAS 413622-10-3), DIPEA (0.60 mL, 3.45 mmol), HOBt (0.19 g, 1.13 mmol) and EDCI (0.28 g, 1.46 mmol) and the mixture was stirred at RT for 4 h. The mixture was diluted with 2 M aqueous HCl and extracted into EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.35 g). LCMS (Method 15): 2.61 min, 522.3 $[M+H]^+$.

**Intermediate 600:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00758]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 599** (0.35 g, 0.61 mmol), triethylamine (0.17 mL, 1.22 mmol) and methanesulfonyl chloride (80 µL, 1.03 mmol) in DCM (10 mL) at 0 °C for 10 min, then RT for 40 min, to provide the title compound (0.37 g). LCMS (Method 12): 2.05 min, 600.2 $[M+H]^+$.

**Intermediate 601:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00759]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 600** (0.37 g, 0.61 mmol), **Intermediate 258** (0.15 g, 0.62 mmol) and $K_2CO_3$ (0.25 g, 1.84 mmol) in MeCN (10 mL) at reflux for 24 h. Purified by reverse phase chromatography (105 g C18, 35-45% MeCN in 0.1% aqueous formic acid) to provide the title compound (0.15 g). LCMS (Method 19): 6.07 min, 738.3 $[M+H]^+$.

**Intermediate 602:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00760]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 601** (0.15 g, 0.18 mmol) in DCE (0.10 L) and Grubbs II (35 mg, 41 µmol) at 50 °C for 3 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.15 g). LCMS (Method 19): 5.78 min, 708.6 $[M-H]^-$.

**Intermediate 603:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00761]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 602** (0.15 g, 0.10 mmol) and 10% palladium on carbon (50 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 3.5 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.13 g). LCMS (Method 11): 2.77 min, 712.1 $[M+H]^+$.

**Intermediate 604:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00762]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 587** (0.25 g, 0.34 mmol), $Pd(PPh_3)_2Cl_2$ (24 mg, 34 µmol), copper(I) iodide (6.5 mg, 34 µmol), triethylamine (0.47 mL, 3.39 mmol) and *N*,*N*-dimethylpropargylamine (0.18 mL, 1.70 mmol, CAS 7223-38-3) in MeCN (5 mL) at 65 °C for 18 h. Additional triethylamine (0.24 mL, 1.70 mmol) and *N*,*N*-dimethylpropargylamine (0.18 mL, 1.70 mmol) were added and stirred at 65 °C for 4 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) and catch and release chromatography (1 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH), to provide the title compound (89 mg). LCMS (Method 15): 2.84 min, 740.3 $[M+H]^+$.

**Intermediate 605:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00763]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 604** (89 mg, 0.12 mmol) and 10% palladium on carbon (13 mg) in ethanol (4 mL) under a hydrogen atmosphere at RT for 6 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH), to provide the title compound (80 mg). LCMS (Method 15): 2.90 min, 744.3 $[M+H]^+$.

**Intermediate 606:** Ethyl (*S*)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00764]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 508** (0.38 g, 0.55 mmol), **Intermediate 200** (0.12 g, 0.66 mmol) and $K_2CO_3$ (0.23 g, 1.66 mmol) in MeCN (5.4 mL) at reflux for 16 h. Purified by flash chromatography (20 g silica, eluting 0-5% (0.5% ammonia MeOH) in DCM) and then by flash chromatography (24 g silica gel, 0-100% EtOAc in petroleum ether) to provide the title compound (0.15 g). LCMS (Method 22): 2.15 min, 706.3 $[M+H]^+$.

**Intermediate 607:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00765]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 606** (0.15 g, 0.17 mmol) in DCE (64 mL) and Grubbs II (11 mg, 13 µmol) at 50 °C for 1.5 h. Purified by flash chromatography (40 g silica gel, eluting 10-60% EtOAc in petroleum ether) to provide the title compound (0.12 g). LCMS (Method 15): 2.68 min, 678.3 $[M+H]^+$.

**Intermediate 608:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00766]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 607** (0.12 g, 0.15 mmol) and 10% palladium on carbon (15 mg) in ethanol (9.5 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (92 mg). LCMS (Method 15): 2.73 min, 680.2 $[M+H]^+$.

**Intermediate 609:** Ethyl (*S*)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00767]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 508** (0.39 g, 0.57 mmol), **Intermediate 332** (0.12 g, 0.68 mmol) and $K_2CO_3$ (0.24 g, 1.71 mmol) in MeCN (5 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica, eluting 0-5% (0.5% ammonia MeOH) in DCM) and then by reverse phase chromatography (32 g C18, 5-90% MeCN in 0.1% aqueous ammonia) to provide the title compound (92 mg). LCMS (Method 22): 2.15 min, 702.3 $[M+H]^+$.

**Intermediate 610:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00768]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 609** (94 mg, 0.12 mmol) in DCE (40 mL) and Grubbs II (7.8 mg, 9 µmol) at 50 °C for 1.5 h. Purified by flash chromatography (24 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (84 mg). LCMS (Method 15): 2.67 min, 674.3 $[M+H]^+$.

**Intermediate 611:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00769]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 610** (84 mg, 0.09 mmol) and 10% palladium on carbon (9.3 mg) in ethanol (8 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (70 mg). LCMS (Method 15): 2.72 min, 676.3 $[M+H]^+$.

**Intermediate 612**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00770]** Prepared in an analogous manner to **Intermediate 3** using 2-bromo-3-methylphenol (0.43 g, 2.27 mmol, CAS 22061-78-5), **Intermediate 377** (1.13 g, 1.89 mmol), $K_3PO_4$ (0.80 g, 3.79 mmol), palladium acetate (43 mg, 0.19 mmol) and tricyclohexyl phosphine (53 mg, 0.19 mmol) in toluene (13 mL) and water (1.6 mL) at 100 °C for 2 h. Purified by flash chromatography (24 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.86 g). LCMS (Method 22): 1.87 min, 456.3 $[M-H]^-$.

**Intermediate 613:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-2'-methyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00771]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 612** (0.68 g, 1.18 mmol), phenyl triflimide (0.42 g, 1.18 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (0.46 g, 1.42 mmol) in DCM (8 mL) at RT for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0–20% EtOAc in petroleum ether) to provide the title compound (0.63 g). LCMS (Method 22): 2.09 min, 588.2 $[M-H]^-$.

**Intermediate 614:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00772]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 613** (0.63 g, 0.99 mmol), 5-hexenylboronic acid (0.19 g, 1.48 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.41

g, 2.97 mmol), palladium acetate (22 mg, 0.10 mmol) and RuPhos (69 mg, 0.15 mmol) in toluene (19 mL) and water (2.1 mL) at 100 °C for 18 h. Additional 5-hexenylboronic acid (63 mg, 0.49 mmol), palladium acetate (11 mg, 0.05 mmol) and RuPhos (35 mg, 0.07 mmol) were added and stirred at 100 °C for 6 h. Purified by flash chromatography (24 g silica gel, eluting 0-10% EtOAc in petroleum ether) to provide the title compound (0.41 g). LCMS (Method 22): 2.27 min, 424.2 $[M\text{-Boc}+H]^+$.

**Intermediate 615:** Ethyl (*S*)-3-amino-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00773]** A suspension of **Intermediate 614** (0.41 g, 0.74 mmol) in 4 M HCl in 1,4-dioxane (1.9 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.42 g). LCMS (Method 22): 2.13 min, 424.2 $[M+H]^+$.

**Intermediate 616:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00774]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 615** (0.42 g, 0.81 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.14 g, 1.22 mmol, CAS 413622-10-3), DIPEA (0.43 mL, 2.49 mmol), HOBt (0.11 g, 0.81 mmol) and EDCI (0.19 g, 0.98 mmol) in MeCN (8 mL) at RT for 18 h. Additional (2*R*)-2-hydroxypent-4-enoic acid (71 mg, 0.61 mmol, CAS 413622-10-3), DIPEA (0.21 mL, 1.22 mmol), HOBt (55 mg, 0.41 mmol) and EDCI (39 mg, 0.20 mmol) were added and stirred at RT for 22 h. Purified by flash chromatography (12 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.22 g). LCMS (Method 22): 2.10 min, 522.2 $[M+H]^+$.

**Intermediate 617:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00775]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 616** (0.22 g, 0.39 mmol), triethylamine (0.11 mL, 0.79 mmol) and methanesulfonyl chloride (46 µL, 0.59 mmol) in DCM (5 mL) at 0 °C for 1 h, to provide the title compound (0.29 g). LCMS (Method 22): 2.12 min, 600.3 $[M+H]^+$.

**Intermediate 618:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00776]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 617** (0.29 g, 0.42 mmol), **Intermediate 258** (0.10 g, 0.42 mmol) and $K_2CO_3$ (0.17 g, 1.25 mmol) in MeCN (7 mL) at reflux for 18 h. Purified by reverse phase chromatography (105 g C18, 40-50%

MeCN in 0.1% aqueous formic acid) to provide the title compound (0.10 g). LCMS (Method 12): 2.25 min, 738.3 $[M+H]^+$.

**Intermediate 619:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00777]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 618** (99 mg, 0.13 mmol) in DCE (55 mL) and Grubbs II (11 mg, 13 µmol) at 50 °C for 2 h. Purified by flash chromatography (4 g silica gel, eluting 0-30% MeOH in DCM) to provide the title compound (91 mg). LCMS (Method 15): 2.83 min, 710.2 $[M+H]^+$; olefin isomerisation metathesis product: 2.72 min, 696.2 $[M-14+H]^+$.

**Intermediate 620:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00778]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 619** (91 mg, 0.13 mmol) and 10% palladium on carbon (20 mg) in ethanol (2 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (92 mg). LCMS (Method 15): 2.85 min, 712.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.75 min, 698.3 $[M-14+H]^+$.

**Intermediate 621:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$2^4$-fluoro-6-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00779]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 593** (0.16 g, 0.15 mmol), 3-fluoroazetidine hydrochloride (20 mg, 0.18 mmol, CAS 617718-46-4), triethylamine (63 µL, 0.45 mmol) in DCM (4.4 mL) and 4 Å molecular sieves at RT for 1.5 h, then STAB (64 mg, 0.30 mmol) at RT for 18 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (64 mg). LCMS (Method 15): 2.76 min, 704.2 $[M+H]^+$.

**Intermediate 622:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$2^4$-fluoro-6-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00780]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 621** (64 mg, 0.09 mmol) and 10% palladium on carbon (10 mg) in ethanol (3 mL) under a hydrogen atmosphere at RT for 6 h. Purified by flash chromatography (12 g silica gel, eluting 5-10%

MeOH in DCM) to provide the title compound (60 mg). LCMS (Method 15): 2.79 min, 706.3 $[M+H]^+$.

**Intermediate 623:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2',4'-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(4-fluoro-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00781]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 382** (0.50 g, 0.81 mmol), 4-fluoro-1*H*-pyridin-2-one (0.12 g, 1.06 mmol, CAS 96530-75-5) and $K_2CO_3$ (0.34 g, 2.44 mmol) in MeCN (5.4 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.11 g). LCMS (Method 15): 2.74 min, 633.2 $[M+H]^+$.

**Intermediate 624:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-$1^4$-fluoro-10-(4-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[00782]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 623** (0.11 g, 0.17 mmol) in DCE (58 mL) and Grubbs II (15 mg, 17 µmol) at 40 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-45% EtOAc in petroleum ether) to provide the title compound (51 mg). LCMS (Method 15): 2.56 min, 605.2 $[M+H]^+$.

**Intermediate 625:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-$1^4$-fluoro-10-(4-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[00783]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 624** (51 mg, 0.08 mmol) and 10% palladium on carbon (9 mg) in ethanol (3 mL) under a hydrogen atmosphere at RT for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (38 mg). LCMS (Method 15): 2.60 min, 607.2 $[M+H]^+$.

**Intermediate 626:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-4-methyl-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00784]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 436** (0.77 g, 1.26 mmol), 5-bromo-4-methylpyridin-2-ol (0.26 g, 1.38 mmol, CAS 164513-38-6) and $K_2CO_3$ (0.52 g, 3.76 mmol) in MeCN (15 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.41 g). LCMS (Method 15): 2.97 min, 707.1 $[M+H]^+$.

**Intermediate 627:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00785]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 626** (0.41 g, 0.58 mmol) in DCE (0.24 L) and Grubbs II (49 mg, 58 µmol) at 45 °C for 2 h. Purified by flash chromatography (24 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.28 g). LCMS (Method 15): 2.89 min, 679.2 $[M+H]^+$.

**Intermediate 628:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-((*E*)-2-ethoxyvinyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00786]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 627** (0.22 g, 0.36 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (71 mg, 0.36 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (24 mg, 32 µmol) and $Na_2CO_3$ (69 mg, 0.65 mmol) in 1,4-dioxane (9 mL) and water (3 mL) at 90 °C for 1 h. Purified by flash chromatography (25 g silica gel, eluting 0-100% EtOAc in petroleum ether), to provide the title compound (0.22 g). LCMS (Method 15): 2.87 min, 669.3 $[M+H]^+$.

**Intermediate 629:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-6-(4-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00787]** A solution of **Intermediate 628** (0.21 g, 0.32 mmol) in DCM (15 mL) and TFA (1.6 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.20 g). LCMS (Method 15): 2.69 min, 641.3 $[M+H]^+$.

**Intermediate 630:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00788]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 629** (0.28 g, 0.15 mmol), azetidine (10 µL, 0.15 mmol), triethylamine (72 µL, 0.52 mmol) in DCM (3 mL) and 4 Å molecular sieves at RT for 3 h, then STAB (93 mg, 0.44 mmol) at RT for 42 h. Purified by catch and release chromatography (1 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (43 mg). LCMS (Method 15): 2.87 min, 682.3 $[M+H]^+$.

**Intermediate 631:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00789]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 630** (46 mg, 0.07 mmol) and 10% palladium on carbon (7 mg) in ethanol (3 mL) under a hydrogen atmosphere at RT for 6 h. Conditions repeated for 4 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (27 mg). LCMS (Method 15): 2.86 min, 684.3 $[M+H]^+$.

**Intermediate 632:** 4,4'-Difluoro-3'-formyl-6-methyl-5'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate

**[00790]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 441** (2.11 g, 6.67 mmol), phenyl triflimide (2.38 g, 6.67 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (2.61 g, 8.01 mmol) in DCM (40 mL) at RT for 2 h. Purified by flash chromatography (25 g silica gel, eluting 20–80% EtOAc in petroleum ether) to provide the title compound (2.09 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 10.45 (s, 1H), 7.96 (dd, 1H), 7.75 (dd, 1H), 7.11 (dd, 1H), 7.03 (dd, 1H), 2.17 (s, 3H).

**Intermediate 633:** 4,4'-Difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carbaldehyde

**[00791]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 632** (2.09 g, 4.65 mmol), 5-hexenylboronic acid (0.89 g, 6.98 mmol, CAS 1072952-16-9), $K_2CO_3$ (1.93 g, 14.0 mmol), palladium acetate (0.10 g, 0.47 mmol) and RuPhos (0.33 g, 0.70 mmol) in toluene (42 mL) and water (5 mL) at 100 °C for 2 h. Purified by flash chromatography (40 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (1.38 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 10.46 (s, 1H), 7.85 (dd, 1H), 7.64 (dd, 1H), 6.84 (d, 2H), 5.73 – 5.62 (m, 1H), 4.95 – 4.87 (m, 2H), 2.27 – 2.22 (m, 2H), 1.97 (s, 3H), 1.91 (q, 2H), 1.43 – 1.37 (m, 2H), 1.27 – 1.23 (m, 2H).

**Intermediate 634:** (*R*,*Z*)-*N*-((4,4'-Difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methylene)-2-methylpropane-2-sulfinamide

**[00792]** Prepared in an analogous manner to **Intermediate 102** using **Intermediate 633** (1.37 g, 3.59 mmol), (*R*)-2-methylpropane-2-sulfinimide (0.48 g, 3.94 mmol) and titanium ethoxide (1.23 g, 5.38 mol) in THF (24 mL) at 40 °C for 2 h, to provide the title compound (1.57 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 8.96 (s, 1H), 7.98 – 7.93 (m, 1H), 7.53 (dd, 1H), 6.85 (dd, 2H), 5.73 – 5.61 (m, 1H), 4.95 – 4.83 (m, 2H), 2.32 – 2.24 (m, 2H), 2.01 (s, 3H), 1.95 – 1.88 (m, 2H), 1.44 – 1.39 (m, 2H), 1.28 – 1.25 (m, 11H).

**Intermediate 635:** Ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00793]** Prepared in an analogous manner to **Intermediate 104** using zinc (1.06 g, 16.1 mmol), chlorotrimethylsilane (82 µL, 0.65 mmol) and ethyl bromoacetate (0.90 mL, 8.07 mmol) in THF (20 mL) at 60 °C for 1 h, then **Intermediate 634** (1.57 g, 3.22 mmol) in THF (12 mL) at RT for 2 h. Purified by flash chromatography (40 g silica gel, eluting 0-80% EtOAc in petroleum ether) to provide the title compound (1.01 g). LCMS (Method 15): 2.82 min, 574.2 $[M+H]^+$.

**Intermediate 636:** Ethyl (*S*)-3-amino-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00794]** A suspension of **Intermediate 635** (1.01 g, 1.76 mmol) in 4 M HCl in 1,4-dioxane (8.8 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure and purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.83 g). LCMS (Method 15): 2.72 min, 470.2 $[M+H]^+$.

**Intermediate 637:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00795]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 636** (0.83 g, 1.76 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.31 g, 2.64 mmol, CAS 413622-10-3), DIPEA (0.92 mL, 5.28 mmol), HOBt (0.26 g, 1.94 mmol) and EDCI (0.41 g, 2.64 mmol) in MeCN (24 mL) at RT for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (0.41 g). LCMS (Method 7): 2.68 min, 568.2 $[M+H]^+$.

**Intermediate 638:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00796]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 637** (0.41 g, 0.72 mmol), triethylamine (0.20 mL, 1.44 mmol) and methanesulfonyl chloride (83 µL, 1.08 mmol) in DCM (8 mL) at 0 °C for 1 h, to provide the title compound (0.51 g). LCMS (Method 15): 2.73 min, 646.1 $[M+H]^+$.

**Intermediate 639:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00797]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 638** (0.51 g, 0.70 mmol), **Intermediate 258** (0.18 g, 0.77 mmol) and $K_2CO_3$ (0.29 g, 2.09 mmol) in MeCN (10 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, 0-60% EtOAc in

petroleum ether) to provide the title compound (0.24 g). LCMS (Method 15): 2.88 min, 784.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.68 min, 742.2 $[M-14+H]^+$.

**Intermediate 640:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00798]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 639** (0.24 g, 0.23 mmol) in DCE (0.15 L) and Grubbs II (19 mg, 23 µmol) at 50 °C for 2.5 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.20 g). LCMS (Method 15): 2.77 min, 756.3 $[M+H]^+$.

**Intermediate 641:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00799]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 640** (0.29 mg, 0.27 mmol) and 10% palladium on carbon (29 mg) in ethanol (2 mL) under a hydrogen atmosphere at RT for 5 h. Conditions repeated for 5 h. Purified by flash chromatography (12 g silica gel, eluting 5-10% MeOH in DCM) to provide the title compound (0.15 g). LCMS (Method 15): 2.80 min, 758.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.71 min, 744.2 $[M-14+H]^+$.

**Intermediate 642:** 3-Fluoro-1-(prop-2-yn-1-yl)azetidine

**[00800]** To a solution of propargyl bromide (2.5 g, 16.8 mmol) in DCM (24 mL) was added 3-fluoroazetidine hydrochloride (3.75 g, 33.6 mmol, CAS 617718-46-4) and triethylamine (4.69 mL, 33.6 mmol) then the mixture was stirred at 30 °C for 4 h. The mixture was diluted with DCM and extracted with 2 M aqueous HCl. The aqueous layer was basified with saturated aqueous $Na_2CO_3$ then extracted with DCM. The organics were washed with brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (3.2 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 5.20 – 4.97 (m, 1H), 3.67 – 3.59 (m, 2H), 3.45 – 3.40 (m, 1H), 3.40 – 3.35 (m, 1H), 3.33 (d, 2H), 2.29 (t, 1H).

**Intermediate 643:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-6-(5-(3-(3-fluoroazetidin-1-yl)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00801]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 587** (0.15 g, 0.20 mmol), $Pd(PPh_3)_2Cl_2$ (14 mg, 20 µmol), copper(I) iodide (3.9 mg, 20 µmol), triethylamine (0.28 mL, 2.03 mmol) and **Intermediate 642** (0.23 g, 2.03 mmol) in MeCN (8 mL) at 65 °C for 18 h. Additional $Pd(PPh_3)_2Cl_2$ (14 mg, 20 µmol), triethylamine (0.28 mL, 2.03 mmol) and **Intermediate 642** (0.23 g, 2.03 mmol) were added and stirred at 65 °C for 24 h.

Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) and catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH), to provide the title compound (0.20 g). LCMS (Method 15): 2.80 min, 770.3 $[M+H]^+$.

**Intermediate 644:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-6-(5-(3-(3-fluoroazetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00802]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 643** (0.20 mg, 0.13 mmol) and 10% palladium on carbon (14 mg) in ethanol (5 mL) under a hydrogen atmosphere at RT for 6 h. Conditions repeated for 5 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.15 g). LCMS (Method 15): 2.84 min, 774.3 $[M+H]^+$.

**Intermediate 645:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4-fluoro-2'-(hex-5-en-1-yl)-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00803]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 560** (1.67 g, 2.39 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.87 g, 3.58 mmol, CAS 109919-32-6) and $K_2CO_3$ (0.99 g, 7.16 mmol) in MeCN (24 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, 0-50% EtOAc in petroleum ether) to provide the title compound (0.84 g). LCMS (Method 22): 2.29 min, 735.2 $[M+H]^+$.

**Intermediate 646:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$,$2^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00804]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 645** (0.75 g, 1.03 mmol) in DCE (0.33 L) and Grubbs II (87 mg, 0.10 mmol) at 50 °C for 1.5 h. Purified by flash chromatography (25 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.51 g). LCMS (Method 22): 2.25 min, 707.6 $[M+H]^+$.

**Intermediate 647:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$,$2^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00805]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 646** (0.51 g, 0.66 mmol) and 10% palladium on carbon (71 mg) in EtOAc (57 mL) under a hydrogen atmosphere at RT for 1.5 h, to provide the title compound (0.41 g). LCMS (Method 15): 2.93 min, 709.3 $[M+H]^+$.

**Intermediate 648:** Ethyl 2-((3*S*,6*S*)-$2^4$-fluoro-$1^4$,$1^6$,$2^5$-trimethyl-5-oxo-6-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00806]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 647** (0.30 g, 0.42 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (91 mg, 0.46 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (31 mg, 42 μmol) and $Na_2CO_3$ (89 mg, 0.84 mmol) in 1,4-dioxane (15 mL) and water (5 mL) at 90 °C for 1.5 h. Additional *trans*-2-ethoxyvinylboronic acid pinacol ester (91 mg, 0.46 mmol) was added and heated at 90 °C for 1.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% EtOAc in petroleum ether). This was dissolved in DCM (13.8 mL) and TFA (1.47 mL) and stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (0.20 g). LCMS (Method 15): 2.94 min, 671.3 $[M+H]^+$.

**Intermediate 649:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$,2$^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00807]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 648** (0.20 g, 0.30 mmol), azetidine (24 μL, 0.36 mmol), triethylamine (0.17 mL, 1.19 mmol) in DCM (3 mL) and 4 Å molecular sieves at RT for 4 h, then STAB (0.13 g, 0.60 mmol) at RT for 16 h. Purified by catch and release chromatography (10 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.12 g). LCMS (Method 15): 2.92 min, 712.3 $[M+H]^+$.

**Intermediate 650:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$,2$^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00808]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 647** (0.30 g, 0.42 mmol), $Pd(PPh_3)_2Cl_2$ (30 mg, 42 μmol), copper(I) iodide (8 mg, 42 μmol), triethylamine (0.59 mL, 4.24 mmol) and *N*,*N*-dimethylpropargylamine (0.23 mL, 2.12 mmol, CAS 7223-38-3) in MeCN (6 mL) at 65 °C for 18 h. Additional triethylamine (0.30 mL, 2.12 mmol), *N*,*N*-dimethylpropargylamine (0.23 mL, 2.12 mmol) and $Pd(PPh_3)_2Cl_2$ (30 mg, 42 μmol) were added and stirred at 65 °C for 4 h. Purified by flash chromatography (12 g silica gel, eluting 0-5% (0.5% ammonia MeOH) in DCM) and catch and release chromatography (10 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH), to provide the title compound (0.30 g). LCMS (Method 15): 2.84 min, 710.3 $[M+H]^+$.

**Intermediate 651:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$,2$^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00809]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 650** (0.18 g, 0.66 mmol) and 10% palladium on carbon (24 mg) in ethanol (7 mL) under a hydrogen

atmosphere at RT for 7 h, to provide the title compound (0.19 g). LCMS (Method 15): 2.96 min, 714.3 $[M+H]^+$.

**Intermediate 652:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00810]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 589** (0.10 g, 0.15 mmol), 3-methoxyazetidine hydrochloride (22 mg, 0.18 mmol), triethylamine (81 µL, 0.58 mmol) in DCM (1.4 mL) and 4 Å molecular sieves at RT for 2 h, then STAB (62 mg, 0.58 mmol) at RT for 18 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (77 mg). LCMS (Method 15): 2.75 min, 772.4 $[M+H]^+$; olefin isomerisation metathesis product: 2.66 min, 758.3 $[M-14+H]^+$.

**Intermediate 653:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00811]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 617** (1.25 g, 2.08 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.66 g, 2.71 mmol, CAS 109919-32-6) and $K_2CO_3$ (0.86 g, 6.25 mmol) in MeCN (17 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, 0-40% EtOAc in petroleum ether) to provide the title compound (0.91 g). LCMS (Method 15): 2.82 min, 747.3 $[M+H]^+$.

**Intermediate 654:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00812]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 653** (0.91 g, 1.12 mmol) in DCE (0.37 L) and Grubbs II (95 mg, 0.11 mmol) at 40 °C for 2 h. Purified by flash chromatography (40 g silica gel, eluting 0-35% EtOAc in petroleum ether) to provide the title compound (0.41 g). LCMS (Method 15): 2.86 min, 717.2 $[M+H]^+$.

**Intermediate 655:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00813]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 654** (0.41 g, 0.57 mmol) and 10% palladium on carbon (61 mg) in EtOAc (40 mL) under a hydrogen atmosphere at RT for 1 h, to provide the title compound (0.31 g). LCMS (Method 15): 2.89 min, 719.2 $[M+H]^+$.

**Intermediate 656:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-((*E*)-2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00814]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 655** (0.26 g, 0.36 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (79 mg, 0.40 mmol, CAS 1201905-61-4), Pd(dppf)$Cl_2$ (26 mg, 36 μmol) and $Na_2CO_3$ (77 mg, 0.72 mmol) in 1,4-dioxane (12 mL) and water (4 mL) at 90 °C for 1 h. Purified by flash chromatography (24 g silica gel, eluting 0-40% EtOAc in petroleum ether), to provide the title compound (0.21 g). LCMS (Method 15): 2.91 min, 711.2 $[M+H]^+$.

**Intermediate 657:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-2$^4$-fluoro-1$^6$-methyl-5-oxo-6-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00815]** A solution of **Intermediate 656** (0.21 g, 0.27 mmol) in DCM (14 mL) and TFA (1.3 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.18 g). LCMS (Method 15): 2.69 min, 683.2 $[M+H]^+$.

**Intermediate 658:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00816]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 657** (0.18 g, 0.27 mmol), azetidine (22 μL, 0.32 mmol), triethylamine (0.15 mL, 1.08 mmol) in DCM (4 mL) and 4 Å molecular sieves at RT for 3 h, then STAB (0.11 g, 0.54 mmol) at RT for 18 h. Purified by catch and release chromatography (1 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.15 g). LCMS (Method 15): 2.90 min, 724.3 $[M+H]^+$.

**Intermediate 659:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00817]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 436** (0.40 g, 0.59 mmol), **Intermediate 332** (0.13 g, 0.70 mmol) and $K_2CO_3$ (0.24 g, 1.76 mmol) in MeCN (5.6 mL) at 65 °C for 36 h. Purified by flash chromatography (24 g silica, eluting 0-10% MeOH in DCM) to provide the title compound (0.15 g). LCMS (Method 15): 2.86 min, 698.3 $[M+H]^+$.

**Intermediate 660:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00818]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 659** (0.17 g, 0.21 mmol) in DCE (69 mL) and Grubbs II (13 mg, 0.07 mmol) at 50 °C for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.12 g). LCMS (Method 15): 2.77 min, 670.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.67 min, 656.3 $[M-14+H]^+$.

**Intermediate 661:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00819]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 660** (0.12 g, 0.12 mmol) and 10% palladium on carbon (13 mg) in ethanol (12 mL) under a hydrogen atmosphere at RT for 3 h. Conditions repeated for 5 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% (0.1% ammonia MeOH) in DCM) to provide the title compound (95 mg). LCMS (Method 15): 2.81 min, 672.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.72 min, 658.3 $[M-14+H]^+$.

**Intermediate 662:** Ethyl (*S*)-3-(3-bromo-5-chlorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

**[00820]** Prepared in an analogous manner to **Intermediate 104** using zinc (9.07 g, 0.14 mol), chlorotrimethylsilane (0.7 mL, 5.55 mmol) and ethyl bromoacetate (11.6 g, 69.3 mmol) in THF (85 mL) at 60 °C for 2 h, then (*R*,*Z*)-*N*-(3-bromo-5-chlorobenzylidene)-2-methylpropane-2-sulfinamide (1.57 g, 3.22 mmol, CAS 2396463-98-0) in THF (26 mL) at RT for 1 h. Purified by dry flash chromatography (silica gel, eluting 20-50% EtOAc in petroleum ether) to provide the title compound (17.0 g). LCMS (Method 22): 1.76 min, 411.9 $[M+H]^+$.

**Intermediate 663:** Ethyl (*S*)-3-amino-3-(3-bromo-5-chlorophenyl)propanoate

**[00821]** A suspension of **Intermediate 662** (9.6 g, 22.2 mmol) in 4 M HCl in 1,4-dioxane (56 mL) was stirred at RT for 7 h. The mixture was diluted with water and washed with EtOAc. The aqueous was basified with aqueous $NaHCO_3$ and extracted with EtOAc. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure, to provide the title compound (6.01 g). LCMS (Method 22): 1.57 min, 307.9 $[M+H]^+$.

**Intermediate 664:** Ethyl (*S*)-3-(3-bromo-5-chloro-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00822]** To a stirred suspension of **Intermediate 663** (3.67 g, 10.8 mmol) and Boc anhydride (2.59 g, 11.9 mmol) in DCM (59 mL) was added triethylamine (2.25 mL, 16.2 mmol) and the mixture stirred for 20 h at RT. The reaction mixture was washed with 1 M aqueous HCl, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was

purified by flash chromatography (120 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (3.6 g). LCMS (Method 22): 1.89 min, 406.0 $[M-H]^-$.

**Intermediate 665:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(3-chloro-5-cyclopropylphenyl)propanoate

**[00823]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 664** (1.63 g, 3.77 mmol), cyclopropaneboronic acid (0.32 g, 3.77 mmol), $K_2CO_3$ (1.56 g, 11.3 mmol), $Pd(dtbpf)Cl_2$ (0.12 g, 0.19 mmol) in toluene (40 mL) at 70 °C for 20 h. Additional cyclopropaneboronic acid (65 mg, 0.75 mmol), $K_2CO_3$ (0.31 g, 2.26 mmol), $Pd(dtbpf)Cl_2$ (38 mg, 0.04 mmol) were added and stirred at 70 °C for 20 h. Purified by dry flash chromatography (silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (1.1 g). LCMS (Method 15): 2.40 min, 366.2 $[M-H]^-$.

**Intermediate 666:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(3-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate

**[00824]** Prepared in an analogous manner to **Intermediate 2** using **Intermediate 665** (1.15 g, 2.81 mmol), bis(pinacolato)diboron (1.43 g, 5.63 mmol), potassium acetate (0.83 g, 8.44 mmol), palladium acetate (63 mg, 0.28 mmol) and SPhos (0.12 g, 0.28 mmol) in DME (27 mL) at 85 °C for 3 h. Purified by flash chromatography (40 g silica gel, eluting 0-10% EtOAc in petroleum ether) to provide the title compound (2.22 g). $^1H$ NMR (400 MHz; $CDCl_3$) δ: 7.48 (d, 1H), 7.41 (d, 1H), 7.10 (d, 1H), 5.34 (s, 1H), 5.06 (s, 1H), 4.13 – 4.03 (m, 2H), 2.89 – 2.71 (m, 2H), 1.94 – 1.83 (m, 1H), 1.42 (s, 9H), 1.33 (s, 12H), 1.19 (t, 3H), 0.97 – 0.88 (m, 2H), 0.74 – 0.65 (m, 2H).

**Intermediate 667**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-2'-hydroxy-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00825]** Prepared in an analogous manner to **Intermediate 3** using 2-bromo-3,5-dimethylphenol (1.33 g, 6.63 mmol, CAS 125237-08-3), **Intermediate 666** (2.03 g, 4.42 mmol), $K_3PO_4$ (1.88 g, 8.84 mmol), palladium acetate (99 mg, 0.44 mmol) and tricyclohexyl phosphine (1.23 g, 0.44 mmol) in toluene (38 mL) and water (5 mL) at 100 °C for 1 h. Purified by flash chromatography (40 g silica gel, eluting 0-15% EtOAc in petroleum ether) to provide the title compound (1.61 g). LCMS (Method 15): 2.44 min, 354.1 $[M\text{-}Boc+H]^+$.

**Intermediate 668:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-2',4'-dimethyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00826]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 667** (1.88 g, 3.81 mmol), phenyl triflimide (1.36 g, 3.81 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (1.49 g, 4.58 mmol) in DCM (25 mL) at RT for 22 h. Purified by flash chromatography (40 g silica gel,

eluting 0–20% EtOAc in petroleum ether) to provide the title compound (2.60 g). LCMS (Method 15): 2.72 min, 584.2 $[M-H]^-$.

**Intermediate 669:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00827]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 668** (2.60 g, 4.22 mmol), 5-hexenylboronic acid (0.81 g, 6.33 mmol, CAS 1072952-16-9), $K_2CO_3$ (1.75 g, 12.7 mmol), palladium acetate (95 mg, 0.42 mmol) and RuPhos (0.30 g, 0.63 mmol) in toluene (81 mL) and water (9 mL) at 100 °C for 7 h. Purified by flash chromatography (40 g silica gel, eluting 0-10% EtOAc in petroleum ether) to provide the title compound (1.94 g). LCMS (Method 15): 2.98 min, 518.3 $[M-H]^-$.

**Intermediate 670:** Ethyl (*S*)-3-amino-3-(5-cyclopropyl-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00828]** A suspension of **Intermediate 669** (1.94 g, 3.40 mmol) in 4 M HCl in 1,4-dioxane (8.6 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (2.2 g). LCMS (Method 15): 2.77 min, 420.2 $[M+H]^+$.

**Intermediate 671:** Ethyl (*S*)-3-(5-cyclopropyl-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00829]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 670** (1.10 g, 1.54 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.27 g, 2.32 mmol, CAS 413622-10-3), DIPEA (0.82 mL, 4.73 mmol), HOBt (0.21 g, 1.54 mmol) and EDCI (0.36 g, 1.85 mmol) in MeCN (15 mL) at RT for 66 h. Purified by flash chromatography (12 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.53 g). LCMS (Method 15): 2.74 min, 518.3 $[M+H]^+$.

**Intermediate 672:** Ethyl (*S*)-3-(5-cyclopropyl-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00830]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 671** (0.53 g, 0.92 mmol), triethylamine (0.26 mL, 1.84 mmol) and methanesulfonyl chloride (0.11 mL, 1.38 mmol) in DCM (12 mL) at RT for 1 h, to provide the title compound (0.78 g). LCMS (Method 15): 2.77 min, 596.3 $[M+H]^+$.

**Intermediate 673:** Ethyl (*S*)-3-(5-cyclopropyl-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00831]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 672** (0.71 g, 1.07 mmol), **Intermediate 258** (0.27 g, 1.08 mmol) and $K_2CO_3$ (0.44 g, 3.21 mmol) in MeCN (18 mL) at reflux for 19 h. Additional **Intermediate 258** (39 mg, 0.16 mmol) and $K_2CO_3$ (66 mg, 0.48 mmol) were added and stirred at reflux for 23 h. Purified by flash chromatography (40 g silica gel, 0-5% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.25 g). LCMS (Method 15): 2.96 min, 734.3 $[M+H]^+$.

**Intermediate 674:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00832]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 673** (0.15 g, 0.19 mmol) in DCE (84 mL) and Grubbs II (16 mg, 0.02 mmol) at 50 °C for 3 h. Purified by flash chromatography (25 g silica gel, eluting 0-40% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.11 g). LCMS (Method 15): 2.84 min, 706.3 $[M+H]^+$.

**Intermediate 675:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00833]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 674** (77 mg, 0.08 mmol) and 10% palladium on carbon (8.5 mg) in ethanol (1 mL) under a hydrogen atmosphere at RT for 4 h. Conditions repeated for 4 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (59 mg). LCMS (Method 15): 2.84 min, 708.4 $[M+H]^+$.

**Intermediate 676:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-4-methyl-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00834]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 508** (1.40 g, 2.06 mmol), 5-bromo-4-methylpyridin-2-ol (0.43 g, 2.27 mmol, CAS 164513-38-6) and $K_2CO_3$ (0.86 g, 6.19 mmol) in MeCN (28 mL) at reflux for 16 h. Purified by flash chromatography (80 g silica, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.79 g). LCMS (Method 15): 2.77 min, 709.5 $[M+H]^+$.

**Intermediate 677:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-4-methyl-2-oxopyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00835]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 676** (0.78 g, 1.07 mmol) in DCE (0.30 L) and Grubbs II (67 mg, 0.08 mmol) at 50 °C for 1.5 h. Purified

by flash chromatography (40 g silica gel, eluting 0-6% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.69 g). LCMS (Method 15): 2.79 min, 683.2 $[M+H]^+$.

**Intermediate 678:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00836]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 677** (0.69 g, 0.66 mmol) and 10% palladium on carbon (70 mg) in ethanol (94 mL) under a hydrogen atmosphere at RT for 2 h. Purified by flash chromatography (40 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.20 g). LCMS (Method 15): 2.83 min, 685.2 $[M+H]^+$.

**Intermediate 679:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-((*E*)-2-ethoxyvinyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00837]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 678** (0.20 g, 0.25 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (54 mg, 0.27 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (18 mg, 25 µmol) and $Na_2CO_3$ (52 mg, 0.49 mmol) in 1,4-dioxane (8 mL) and water (3 mL) at 90 °C for 1 h. Purified by flash chromatography (24 g silica gel, eluting 0-40% EtOAc in petroleum ether), to provide the title compound (0.19 g). LCMS (Method 15): 2.82 min, 675.3 $[M+H]^+$.

**Intermediate 680:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-6-(4-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00838]** A solution of **Intermediate 679** (0.19 g, 0.27 mmol) in DCM (13 mL) and TFA (1.4 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.16 g). LCMS (Method 15): 2.59 min, 647.3 $[M+H]^+$.

**Intermediate 681:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00839]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 680** (0.16 g, 0.27 mmol), azetidine (13 µL, 0.19 mmol), triethylamine (0.18 mL, 1.29 mmol) in DCM (6 mL) and 4 Å molecular sieves at RT for 4 h, then STAB (69 mg, 0.32 mmol) at RT for 16 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.12 g). LCMS (Method 15): 2.83 min, 688.3 $[M+H]^+$.

**Intermediate 682:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-6-(4-methyl-2-oxopyridin-1(2*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00840]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 677** (0.69 g, 0.66 mmol) and 10% palladium on carbon (70 mg) in ethanol (94 mL) under a hydrogen atmosphere at RT for 2 h. Purified by flash chromatography (40 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.11 g). LCMS (Method 15): 2.68 min, 605.3 $[M+H]^+$.

**Intermediate 683:** (*R*,*Z*)-*N*-(5-Bromo-2-chlorobenzylidene)-2-methylpropane-2-sulfinamide

**[00841]** Prepared in an analogous manner to **Intermediate 102** using 5-bromo-2-chloro-benzaldehyde (10 g, 45.6 mmol, CAS 189628-37-3), (*R*)-2-methylpropane-2-sulfinimide (9.38 g, 77.4 mmol, CAS 196929-78-9) and titanium ethoxide (15.6 g, 68.4 mmol) in THF (74 mL) at 40 °C for 16 h, to provide the title compound (15.0 g). LCMS (Method 12): 1.76 min, 324.0 $[M+H]^+$.

**Intermediate 684:** Ethyl (*S*)-3-(5-bromo-2-chlorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

**[00842]** Prepared in an analogous manner to **Intermediate 104** using zinc (13.8 g, 0.21 mol), chlorotrimethylsilane (1.07 mL, 8.43 mmol) and ethyl bromoacetate (17.6 g, 0.11 mol) in THF (0.15 L) at 65 °C for 2 h, then **Intermediate 683** (15.0 g, 42.2 mmol) in THF (43 mL) at RT for 1 h. Purified by dry flash chromatography (silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (7.5 g). LCMS (Method 11): 2.05 min, 412.0 $[M+H]^+$.

**Intermediate 685:** Ethyl (*S*)-3-amino-3-(5-bromo-2-chlorophenyl)propanoate

**[00843]** A suspension of **Intermediate 684** (7.5 g, 17.3 mmol) in 4 M HCl in 1,4-dioxane (26 mL) and ethanol (75 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure, diluted with water and washed with EtOAc. The aqueous was basified with aqueous $NaHCO_3$ and extracted with EtOAc. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure, to provide the title compound (5.2 g). LCMS (Method 15): 1.88 min, 307.9 $[M+H]^+$.

**Intermediate 686:** Ethyl (*S*)-3-(5-bromo-2-chlorophenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00844]** To a stirred suspension of **Intermediate 685** (5.2 g, 16.3 mmol) and Boc anhydride (4.26 g, 19.5 mmol) in DCM (50 mL) was added DIPEA (3.16 g, 24.4 mmol) and the mixture stirred for 48 h at RT. The reaction mixture was washed with 1 M aqueous HCl, brine, dried

over $Na_2SO_4$, filtered and concentrated under reduced pressure, to provide the title compound (5.2 g). LCMS (Method 15): 2.33 min, 406.0 $[M-H]^-$.

**Intermediate 687:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate

**[00845]** Prepared in an analogous manner to **Intermediate 2** using **Intermediate 686** (3.64 g, 8.95 mmol), bis(pinacolato)diboron (4.55 g, 17.9 mmol), potassium acetate (2.64 g, 26.9 mmol), $Pd(dppf)Cl_2$ (0.65 g, 0.90 mmol) in 1,4-dioxane (37 mL) at 85 °C for 2 h. Purified by flash chromatography (40 g silica gel, eluting 0-25% EtOAc in petroleum ether) to provide the title compound (4.51 g). $^1H$ NMR (400 MHz; $CDCl_3$) δ: 7.75 (s, 1H), 7.62 (d, 1H), 7.35 (d, 1H), 5.65 (s, 1H), 5.47 (s, 1H), 4.11 – 4.04 (m, 2H), 2.82 (s, 2H), 1.42 (s, 9H), 1.33 (s, 12H), 1.18 (t, 3H).

**Intermediate 688**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-chloro-2'-hydroxy-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00846]** Prepared in an analogous manner to **Intermediate 3** using 2-bromo-3,5-dimethylphenol (1.52 g, 7.56 mmol, CAS 125237-08-3), **Intermediate 687** (2.86 g, 5.04 mmol), $K_3PO_4$ (2.14 g, 10.1 mmol), palladium acetate (0.11 g, 0.50 mmol) and tricyclohexyl phosphine (0.14 g, 0.50 mmol) in toluene (34 mL) and water (14 mL) at 100 °C for 1 h. Purified by flash chromatography (80 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (2.15 g). LCMS (Method 15): 2.38 min, 446.2 $[M-H]^-$.

**Intermediate 689:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-chloro-2',4'-dimethyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00847]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 688** (3.84 g, 7.54 mmol), phenyl triflimide (2.70 g, 7.54 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (2.95 g, 9.05 mmol) in DCM (53 mL) at RT for 20 h. Purified by flash chromatography (40 g silica gel, eluting 0–15% EtOAc in petroleum ether) to provide the title compound (4.20 g). LCMS (Method 15): 2.68 min, 578.2 $[M-H]^-$.

**Intermediate 690:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-chloro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00848]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 689** (0.50 g, 0.78 mmol), 5-hexenylboronic acid (0.15 g, 1.18 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.33 g, 2.53 mmol), palladium acetate (18 mg, 0.08 mmol) and RuPhos (51 mg, 0.15 mmol) in toluene (5 mL) and water (0.5 mL) at 100 °C for 2 h. Purified by flash chromatography (25 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.28 g). LCMS (Method 15): 2.94 min, 414.2 $[M-Boc+H]^+$.

**Intermediate 691:** Ethyl (*S*)-3-amino-3-(4-chloro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00849]** A suspension of **Intermediate 690** (2.10 g, 3.31 mmol) in 4 M HCl in 1,4-dioxane (8.3 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (2.2 g). LCMS (Method 15): 2.77 min, 414.2 $[M+H]^+$.

**Intermediate 692:** Ethyl (*S*)-3-(4-chloro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00850]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 691** (2.20 g, 2.74 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.68 g, 5.57 mmol, CAS 413622-10-3), DIPEA (1.98 mL, 11.1 mmol), HOBt (0.50 g, 3.71 mmol) and EDCI (0.85 g, 4.45 mmol) in MeCN (38 mL) at RT for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (1.54 g). LCMS (Method 15): 2.69 min, 512.3 $[M+H]^+$.

**Intermediate 693:** Ethyl (*S*)-3-(4-chloro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00851]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 692** (0.50 g, 0.89 mmol), triethylamine (0.25 mL, 1.77 mmol) and methanesulfonyl chloride (83 µL, 1.07 mmol) in DCM (10 mL) at RT for 1 h. Additional triethylamine (49 µL, 0.36 mmol) and methanesulfonyl chloride (17 µL, 0.24 mmol) were added and stirred at RT for 1 h, to provide the title compound (0.58 g). LCMS (Method 15): 2.73 min, 588.3 $[M-H]^-$.

**Intermediate 694:** Ethyl (*S*)-3-(4-chloro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00852]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 693** (0.58 g, 0.83 mmol), **Intermediate 258** (0.29 g, 1.24 mmol) and $K_2CO_3$ (0.34 g, 2.48 mmol) in MeCN (13 mL) at reflux for 19 h. Purified by flash chromatography (40 g silica gel, 0-6% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.13 g). LCMS (Method 15): 2.91 min, 728.3 $[M+H]^+$.

**Intermediate 695:** Ethyl 2-((3*S*,6*S*)-2$^4$-chloro-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00853]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 694** (0.13 g, 0.15 mmol) in DCE (73 mL) and Grubbs II (13 mg, 15 µmol) at 50 °C for 1 h. Conditions repeated. Purified by flash chromatography (12 g silica gel, eluting 0-6% (0.1% ammonia

MeOH) in DCM) to provide the title compound (85 mg). LCMS (Method 12): 2.76 min, 700.0 $[M+H]^+$.

**Intermediate 696:** Ethyl 2-((3*S*,6*S*)-$2^4$-chloro-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00854]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 695** (75 mg, 0.09 mmol) and 10% palladium on carbon (15 mg) in ethanol (13 mL) under a hydrogen atmosphere at RT for 1 h. Purified by flash chromatography (12 g silica gel, eluting 0-6% (0.5% ammonia MeOH) in DCM) to provide the title compound (60 mg). LCMS (Method 15): 2.81 min, 702.3 $[M+H]^+$.

**Intermediate 697:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(3-(dimethylamino)prop-1-yn-1-yl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00855]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 677** (0.11 g, 0.09 mmol), $Pd(PPh_3)_2Cl_2$ (6 mg, 9 µmol), copper(I) iodide (1.7 mg, 9 µmol), triethylamine (0.12 mL, 0.87 mmol) and *N*,*N*-dimethylpropargylamine (94 µL, 0.87 mmol, CAS 7223-38-3) in MeCN (3 mL) at 80 °C for 16 h. Purified by flash chromatography (25 g silica gel, eluting 0-100% EtOAc in petroleum ether), to provide the title compound (80 mg). LCMS (Method 15): 2.61 min, 684.3 $[M+H]^+$.

**Intermediate 698:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(3-(dimethylamino)propyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00856]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 697** (80 mg, 0.12 mmol) and 10% palladium on carbon (12 mg) in ethanol (8.5 mL) under a hydrogen atmosphere at RT for 16 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% 1% ammonia MeOH in DCM) to provide the title compound (30 mg). LCMS (Method 15): 2.72 min, 690.3 $[M+H]^+$.

**Intermediate 699:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00857]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 508** (0.68 g, 1.11 mmol), 5-bromo-3-fluoropyridin-2-ol (0.23 g, 1.22 mmol, CAS 156772-63-3) and $K_2CO_3$ (0.46 g, 3.32 mmol) in MeCN (14 mL) at reflux for 16 h. Purified by flash chromatography (40

g silica, eluting 0-80% EtOAc in petroleum ether) to provide the title compound (0.43 g). LCMS (Method 15): 2.78 min, 715.2 $[M+H]^+$.

**Intermediate 700:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00858]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 699** (0.43 g, 0.60 mmol) in DCE (0.35 L) and Grubbs II (51 mg, 60 µmol) at 50 °C for 2 h. Conditions repeated. Purified by flash chromatography (25 g silica gel, eluting 20-100% EtOAc in petroleum ether) to provide the title compound (0.39 g). LCMS (Method 7): 2.74 min, 687.1 $[M+H]^+$.

**Intermediate 701:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-((*E*)-2-ethoxyvinyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00859]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 700** (0.39 g, 0.31 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (64 mg, 0.32 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (22 mg, 31 µmol) and $Na_2CO_3$ (65 mg, 0.61 mmol) in 1,4-dioxane (7.5 mL) and water (2.5 mL) at 85 °C for 1 h. Purified by flash chromatography (40 g silica gel, eluting 0-100% EtOAc in petroleum ether), to provide the title compound (0.19 g). LCMS (Method 15): 2.78 min, 677.3 $[M+H]^+$.

**Intermediate 702:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-6-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00860]** A solution of **Intermediate 701** (0.19 g, 0.27 mmol) in DCM (5.6 mL) and TFA (0.43 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.30 g). LCMS (Method 12): 1.93 min, 649.3 $[M+H]^+$.

**Intermediate 703:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00861]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 702** (0.30 g, 0.28 mmol), azetidine (22 µL, 0.33 mmol), triethylamine (0.12 mL, 0.83 mmol) in DCM (5 mL) and 4 Å molecular sieves at RT for 1.5 h, then STAB (0.12 g, 0.55 mmol) at RT for 16 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.16 g). LCMS (Method 7): 2.05 min, 690.3 $[M+H]^+$.

**Intermediate 704:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00862]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 703** (0.16 g, 0.13 mmol) and 10% palladium on carbon (14 mg) in ethanol (7.5 mL) under a hydrogen atmosphere at RT for 6 h. Purified by flash chromatography (12 g silica gel, eluting 5-10% MeOH in DCM) to provide the title compound (0.15 g). LCMS (Method 15): 2.67 min, 692.3 $[M+H]^+$.

**Intermediate 705:** (*E*)-4-Chloro-5-(2-ethoxyvinyl)-2-methoxypyridine

**[00863]** Prepared in an analogous manner to **Intermediate 364** using 5-bromo-4-chloro-2-methoxypyridine (2.0 g, 8.99 mmol, CAS 851607-27-7), *trans*-2-ethoxyvinylboronic acid pinacol ester (1.96 g, 9.89 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (0.66 g, 0.90 mmol) and $K_3PO_4$ (3.82 g, 18.0 mmol) in 1,4-dioxane (32 mL) and water (3.2 mL) at 50 °C for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-10% EtOAc in petroleum ether), to provide the title compound (1.08 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 8.09 (s, 1H), 6.84 (d, 1H), 6.77 (s, 1H), 5.88 (d, 1H), 4.00 – 3.88 (m, 5H), 1.36 (t, 3H).

**Intermediate 706:** (*E*)-4-Cyclopropyl-5-(2-ethoxyvinyl)-2-methoxypyridine

**[00864]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 705** (1.08 g, 5.06 mmol), cyclopropaneboronic acid (0.56 g, 6.57 mmol), $K_2CO_3$ (2.10 g, 15.2 mmol), palladium acetate (0.11 g, 0.51 mmol) and SPhos (0.31 g, 0.76 mmol) in 1,4-dioxane (20 mL) and water (2 mL) at 85 °C for 16 h. Additional cyclopropaneboronic acid (0.22 g, 2.53 mmol), palladium acetate (57 mg, 0.25 mmol) and SPhos (0.15 g, 0.35 mmol) were added and stirred at 85 °C for 3 h. Purified by reverse phase chromatography (38 g C18, eluting 0-60% MeCN in 0.1% aqueous ammonia) to provide the title compound (0.50 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.96 (s, 1H), 6.71 (d, 1H), 6.24 (s, 1H), 6.00 (d, 1H), 3.97 – 3.90 (m, 2H), 3.88 (s, 3H), 1.95 – 1.84 (m, 1H), 1.36 (t, 3H), 1.04 – 0.93 (m, 2H), 0.74 – 0.65 (m, 2H).

**Intermediate 707:** 2-(4-Cyclopropyl-6-methoxypyridin-3-yl)acetaldehyde

**[00865]** A solution of **Intermediate 706** (0.50 g, 2.29 mmol) in TFA (2.8 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure and azeotroped with DCM to provide the title compound (0.44 g). LCMS (Method 15): 1.43 min, 192.0 $[M+H]^+$.

**Intermediate 708:** 2-(4-Cyclopropyl-6-methoxypyridin-3-yl)-*N*,*N*-dimethylethan-1-amine

**[00866]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 707** (0.40 g, 2.10 mmol), dimethylamine (2 M in THF, 1.26 mL, 2.52 mmol), triethylamine (0.41 mL, 2.94 mmol) in DCM (12.5 mL) and 4 Å molecular sieves at RT for 20 min, then STAB (0.89 g, 4.19

mmol) at RT for 16 h. Purified by flash chromatography (12 g silica gel, eluting 0-20% 1% ammonia MeOH in DCM) to provide the title compound (0.27 g). LCMS (Method 11): 1.70 min, 221.2 $[M+H]^+$.

**Intermediate 709:** 4-Cyclopropyl-5-(2-(dimethylamino)ethyl)pyridin-2(1*H*)-one

**[00867]** A solution of **Intermediate 708** (0.27 g, 1.23 mmol) in 33% HBr in AcOH (8.46 mL, 49.0 mmol) was stirred at 85 °C for 2 h. The mixture was cooled and concentrated under reduced pressure. Conditions repeated at 85 °C for 4 h. The crude product was purified by catch and release chromatography (10 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.19 g). LCMS (Method 11): 1.14 min, 207.2 $[M+H]^+$.

**Intermediate 710:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(4-cyclopropyl-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00868]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 436** (0.45 g, 0.74 mmol), **Intermediate 709** (0.17 g, 0.81 mmol) and $K_2CO_3$ (0.30 g, 2.20 mmol) in MeCN (9 mL) at 85 °C for 16 h. Purified by flash chromatography (25 g silica, eluting 0-6% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.18 g). LCMS (Method 11): 2.91 min, 722.7 $[M-H]^-$.

**Intermediate 711:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(4-cyclopropyl-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00869]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 710** (0.18 g, 0.25 mmol) in DCE (0.11 L) and Grubbs II (21 mg, 25 µmol) at 50 °C for 1 h. Conditions repeated. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.10 g). LCMS (Method 11): 2.74 min, 696.4 $[M+H]^+$.

**Intermediate 712:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(4-cyclopropyl-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00870]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 711** (0.15 g, 0.21 mmol) and 10% palladium on carbon (23 mg) in ethanol (19 mL) under a hydrogen atmosphere at RT for 6 h. Repeated with 10% palladium on carbon (2 mg) in ethanol (19 mL) under a hydrogen atmosphere at RT for 4 h, to provide the title compound (0.13 g). LCMS (Method 15): 2.80 min, 698.4 $[M+H]^+$.

**Intermediate 713:** Ethyl 2-((3*S*,6*S*)-6-(3-chloro-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00871]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1139** (0.26 g, 0.36 mmol) and 10% palladium on carbon (38 mg) in EtOAc (35 mL) under a hydrogen atmosphere at RT for 3 h, to provide the title compound (0.26 g). LCMS (Method 15): 2.83 min, 722.1 $[M+H]^+$.

**Intermediate 714:** Ethyl 2-((3*S*,6*S*)-6-(3-((*E*)-2-ethoxyvinyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00872]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 713** (0.21 g, 0.25 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (54 mg, 0.27 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (18 mg, 25 µmol) and $Na_2CO_3$ (52 mg, 0.49 mmol) in toluene (4.4 mL) and water (1.5 mL) at 90 °C for 4 h. Purified by flash chromatography (25 g silica gel, eluting 0-25% EtOAc in petroleum ether), to provide the title compound (96 mg). LCMS (Method 15): 2.88 min, 758.3 $[M+H]^+$.

**Intermediate 715:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00873]** Prepared in an analogous manner to **Intermediate 1107** using **Intermediate 714** (88 mg, 0.12 mmol), in DCM (1.2 mL) and TFA (0.2 mL) at RT for 1 h. Then 3-methoxyazetidine hydrochloride (17 mg, 0.14 mmol, CAS 148644-09-1), triethylamine (49 µL, 0.35 mmol) in DCM (1.2 mL) with 4 Å molecular sieves at RT for 1 h, followed by STAB (49 mg, 0.23 mmol) at RT for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (40 mg). LCMS (Method 22): 2.13 min, 801.3 $[M+H]^+$.

**Intermediate 716:** Ethyl (*S*)-3-((*S*)-2-(5-(2-morpholinoethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00874]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 997** (0.40 g, 0.55 mmol), **Intermediate 1092** (0.17 g, 0.61 mmol) and $K_2CO_3$ (0.23 g, 1.65 mmol) in MeCN (7 mL) at reflux for 16 h. Purified by reverse phase chromatography (32 g C18, eluting 30-70% MeCN in aqueous formic acid) to provide the title compound (87 mg). LCMS (Method 22): 2.14 min, 830.3 $[M+H]^+$.

**Intermediate 717:** Ethyl 2-((3*S*,6*S*)-$1^4$,$1^6$,$2^4$-trifluoro-6-(5-(2-morpholinoethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00875]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 716** (87 mg, 0.11 mmol) in DCE (35 mL) and Grubbs II (9 mg, 10 µmol) at 50 °C for 1 h. Conditions repeated. Purified by flash chromatography (12 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (41 mg). LCMS (Method 22): 2.07 min, 802.3 $[M+H]^+$.

**Intermediate 718:** Ethyl 2-((3*S*,6*S*)-$1^4$,$1^6$,$2^4$-trifluoro-6-(5-(2-morpholinoethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00876]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 717** (49 mg, 57 µmol) and 10% palladium on carbon (6 mg) in ethanol (6 mL) under a hydrogen atmosphere at RT for 2 h, to provide the title compound (47 mg). LCMS (Method 22): 2.10 min, 804.3 $[M+H]^+$.

**Intermediate 719:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00877]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 638** (0.48 g, 0.75 mmol), **Intermediate 137** (0.12 g, 0.75 mmol) and $K_2CO_3$ (0.31 g, 2.24 mmol) in MeCN (12 mL) at reflux for 18 h. Purified by flash chromatography (24 g silica gel, eluting 2-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.15 g). LCMS (Method 15): 2.73 min, 716.3 $[M+H]^+$.

**Intermediate 720:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00878]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 719** (0.15 g, 0.21 mmol) in DCE (58 mL) and Grubbs II (17 mg, 21 µmol) at 50 °C for 1 h. Conditions repeated. Purified by flash chromatography (12 g silica gel, eluting 2-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.11 g). LCMS (Method 15): 2.63 min, 688.4 $[M+H]^+$.

**Intermediate 721:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-4-methyl-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-4-fluoro-2'-(hex-5-en-1-yl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00879]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 436** (0.45 g, 0.59 mmol), 5-bromo-4-methylpyridin-2-ol (0.12 g, 0.65 mmol, CAS 164513-38-6) and $K_2CO_3$ (0.24 g, 1.76 mmol) in MeCN (8 mL) at 85 °C for 16 h. Purified by flash chromatography (80 g silica, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.21 g). LCMS (Method 15): 2.95 min, 707.2 $[M+H]^+$.

**Intermediate 722:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00880]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 721** (0.21 g, 0.28 mmol) in DCE (79 mL) and Grubbs II (18 mg, 21 µmol) at 50 °C for 1.5 h. Conditions repeated. Purified by flash chromatography (24 g silica gel, eluting 10-60% EtOAc in petroleum ether) to provide the title compound (0.17 g). LCMS (Method 15): 2.84 min, 679.2 $[M+H]^+$.

**Intermediate 723:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(3-(dimethylamino)prop-1-yn-1-yl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00881]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 722** (0.17 g, 0.21 mmol), $Pd(PPh_3)_2Cl_2$ (15 mg, 21 µmol), copper(I) iodide (4 mg, 21 µmol), triethylamine (0.30 mL, 2.13 mmol) and *N*,*N*-dimethylpropargylamine (0.23 mL, 2.13 mmol, CAS 7223-38-3) in MeCN (3.4 mL) at 80 °C for 16 h. Additional $Pd(PPh_3)_2Cl_2$ (7.5 mg, 11 µmol), copper(I) iodide (2 mg, 11 µmol), and *N*,*N*-dimethylpropargylamine (69 µL, 0.64 mmol) were added and heated at 85 °C for 20 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (0.15 g). LCMS (Method 15): 2.76 min, 680.4 $[M+H]^+$.

**Intermediate 724:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(3-(dimethylamino)propyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00882]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 723** (0.15 g, 0.14 mmol) and 10% palladium on carbon (15 mg) in ethanol (16 mL) under a hydrogen atmosphere at RT for 5 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (97 mg). LCMS (Method 15): 2.77 min, 684.4 $[M+H]^+$.

**Intermediate 725:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(3-(dimethylamino)propyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00883]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 724** (97 mg, 0.09 mmol) and 10% palladium on carbon (10 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 10 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (36 mg). LCMS (Method 15): 2.81 min, 686.3 $[M+H]^+$.

**Intermediate 726:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00884]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 655** (0.33 g, 0.45 mmol), $Pd(PPh_3)_2Cl_2$ (22 mg, 32 µmol), copper(I) iodide (6 mg, 32 µmol), triethylamine (0.44 mL, 3.17 mmol) and *N*,*N*-dimethylpropargylamine (0.34 mL, 3.17 mmol, CAS 7223-38-3) in MeCN (9 mL) at 80 °C for 16 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM), to provide the title compound (0.22 g). LCMS (Method 15): 2.79 min, 722.3 $[M+H]^+$.

**Intermediate 727:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00885]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 726** (0.22 g, 0.31 mmol) and 10% palladium on carbon (33 mg) in ethanol (7.5 mL) under a hydrogen atmosphere at RT for 5 h. Purified by catch and release chromatography (2 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.13 g). LCMS (Method 15): 2.88 min, 726.3 $[M+H]^+$.

**Intermediate 728:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(3-(dimethylamino)prop-1-yn-1-yl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00886]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 592** (0.16 g, 0.23 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg, 16 µmol), copper(I) iodide (3 mg, 16 µmol), triethylamine (0.22 mL, 1.59 mmol) and *N*,*N*-dimethylpropargylamine (0.17 mL, 1.59 mmol, CAS 7223-38-3) in MeCN (4 mL) at 80 °C for 16 h. Purified by catch and release chromatography (2 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.15 g). LCMS (Method 15): 2.78 min, 684.3 $[M+H]^+$.

**Intermediate 729:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(3-(dimethylamino)propyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00887]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 728** (0.15 g, 0.23 mmol) and 10% palladium on carbon (19 mg) in ethanol (5 mL) under a hydrogen atmosphere at RT for 6 h. Conditions repeated. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (41 mg). LCMS (Method 15): 2.87 min, 690.4 $[M+H]^+$.

**Intermediate 730:** Ethyl (*S*)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(4-cyclopropyl-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00888]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 508** (0.53 g, 0.86 mmol), **Intermediate 709** (0.20 g, 0.95 mmol) and $K_2CO_3$ (0.36 g, 2.58 mmol) in MeCN (11 mL) at 85 °C for 16 h. Purified by flash chromatography (40 g silica, eluting 3-5% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.11 g). LCMS (Method 11): 2.77 min, 728.3 $[M+H]^+$.

**Intermediate 731:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(4-cyclopropyl-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00889]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 730** (0.11 g, 0.14 mmol) in DCE (72 mL) and Grubbs II (12 mg, 14 µmol) at 50 °C for 2 h. Additional Grubbs II (12 mg, 14 µmol) was added and heated at 50 °C for 1.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (86 mg). LCMS (Method 15): 2.66 min, 700.3 $[M+H]^+$.

**Intermediate 732:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(4-cyclopropyl-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00890]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 731** (86 mg, 76 µmol) and 10% palladium on carbon (8 mg) in ethanol (4 mL) under a hydrogen atmosphere at RT for 7 h. Purified by flash chromatography (12 g silica gel, eluting 5-10% MeOH in DCM) to provide the title compound (55 mg). LCMS (Method 15): 2.71 min, 702.4 $[M+H]^+$.

**Intermediate 733:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(3-(dimethylamino)prop-1-yn-1-yl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00891]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 700** (0.16 g, 0.17 mmol), $Pd(PPh_3)_2Cl_2$ (8.5 mg, 12 µmol), copper(I) iodide (2.3 mg, 12 µmol), triethylamine (0.17 mL, 1.21 mmol) and *N*,*N*-dimethylpropargylamine (0.13 mL, 1.21 mmol, CAS 7223-38-3) in MeCN (3.5 mL) at 80 °C for 4 h. Purified by flash chromatography (12 g

silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.14 g). LCMS (Method 15): 2.71 min, 688.3 $[M+H]^+$.

**Intermediate 734:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(3-(dimethylamino)propyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00892]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 733** (0.14 g, 0.15 mmol) and 10% palladium on carbon (16 mg) in ethanol (8.5 mL) under a hydrogen atmosphere at RT for 4 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (69 mg). LCMS (Method 15): 2.80 min, 694.4 $[M+H]^+$.

**Intermediate 735**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-chloro-5-cyclopropyl-4,4',6'-trifluoro-[1,1'-biphenyl]-3-yl)propanoate

**[00893]** Prepared in an analogous manner to **Intermediate 3** using 2-bromo-1-chloro-3,5-diflourobenzene (0.43 g, 1.89 mmol, CAS 1020198-58-6), **Intermediate 377** (0.60 g, 1.26 mmol), $K_3PO_4$ (0.80 g, 3.77 mmol), potassium formate (0.11 g, 1.26 mmol) and $Pd(dtbpf)Cl_2$ (41 mg, 0.06 mmol) in toluene (7.5 mL) and water (1.3 mL) at 70 °C for 10 h. Purified by flash chromatography (40 g silica gel, eluting 0-25% EtOAc in petroleum ether) to provide the title compound (0.54 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.06 – 7.03 (m, 2H), 6.82 (ddd, 1H), 6.72 (dd, 1H), 5.72 (br s, 1H), 5.37 (br s, 1H), 4.10 – 4.00 (m, 2H), 2.92 – 2.80 (m, 2H), 2.16 – 2.09 (m, 1H), 1.41 (s, 9H), 1.16 (t, 3H), 1.03 – 0.97 (m, 2H), 0.76 – 0.67 (m, 2H).

**Intermediate 736:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)propanoate

**[00894]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 735** (0.67 g, 1.34 mmol), 5-hexenylboronic acid (0.26 g, 2.00 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.55 g, 4.01 mmol), palladium acetate (30 mg, 0.13 mmol) and SPhos (0.11 g, 0.27 mmol) in toluene (12 mL) and water (3 mL) at 90 °C for 4 h. Purified by flash chromatography (24 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.65 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 6.95 (dd, 1H), 6.78 (d, 1H), 6.68 (td, 1H), 6.61 (dd, 1H), 5.73 – 5.64 (m, 1H), 5.35 (br s, 1H), 4.94 – 4.89 (m, 2H), 4.09 – 4.01 (m, 2H), 2.89 – 2.82 (m, 2H), 2.43 – 2.33 (m, 2H), 2.16 – 2.09 (m, 1H), 1.93 (dd, 2H), 1.47 – 1.33 (m, 11H), 1.25 (dd, 2H), 1.17 (t, 3H), 1.04 – 0.95 (m, 2H), 0.74 – 0.65 (s, 2H) – NH not observed.

**Intermediate 737:** Ethyl (*S*)-3-amino-3-(5-cyclopropyl-2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00895]** A suspension of **Intermediate 736** (0.88 g, 1.53 mmol) in 4 M HCl in 1,4-dioxane (5.7 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure to provide the title compound (0.74 g). LCMS (Method 15): 1.93 min, 446.1 $[M+H]^+$.

**Intermediate 738:** Ethyl (*S*)-3-(5-cyclopropyl-2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00896]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 737** (0.74 g, 1.46 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.25 g, 2.19 mmol, CAS 413622-10-3), DIPEA (0.78 mL, 4.38 mmol), HOBt (0.20 g, 1.46 mmol) and EDCI (0.34 g, 1.75 mmol) in MeCN (12 mL) at RT for 20 h. Purified by flash chromatography (25 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.68 g). LCMS (Method 15): 2.58 min, 544.2 $[M+H]^+$.

**Intermediate 739:** Ethyl (*S*)-3-(5-cyclopropyl-2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00897]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 738** (0.68 g, 1.21 mmol), triethylamine (0.34 mL, 2.43 mmol) and methanesulfonyl chloride (0.14 mL, 1.82 mmol) in DCM (11 mL) at RT for 1 h, to provide the title compound (0.75 g). LCMS (Method 15): 2.63 min, 622.3 $[M+H]^+$.

**Intermediate 740:** Ethyl (*S*)-3-(5-cyclopropyl-2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00898]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 739** (0.75 g, 1.17 mmol), **Intermediate 258** (0.33 g, 1.40 mmol) and $K_2CO_3$ (0.49 g, 3.51 mmol) in MeCN (12 mL) at reflux for 24 h. Purified by flash chromatography (40 g silica gel, 0-5% (0.5% ammonia MeOH) in DCM) and reverse phase chromatography (38 g C18, 30-50% MeCN in 0.1% aqueous formic acid) to provide the title compound (0.21 g). LCMS (Method 15): 2.83 min, 760.3 $[M+H]^+$.

**Intermediate 741:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$,2$^4$-trifluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00899]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 740** (0.13 g, 0.12 mmol) in DCE (28 mL) and Grubbs II (10 mg, 12 µmol) at 50 °C for 2.5 h. Additional Grubbs II (12 mg, 14 µmol) was added and heated at 50 °C for 1.5 h. Purified by flash chromatography (24 g silica gel, eluting 0-5% (0.5% ammonia MeOH) in DCM) to provide the title compound (88 mg). LCMS (Method 15): 2.71 min, 732.3 $[M+H]^+$.

**Intermediate 742:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$,2$^4$-trifluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00900]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 741** (88 mg, 0.08 mmol) and 10% palladium on carbon (8.3 mg) in ethanol (6 mL) under a hydrogen atmosphere at RT for 4 h, to provide the title compound (57 mg). LCMS (Method 15): 2.74 min, 734.3 $[M+H]^+$.

**Intermediate 743:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-2$^4$-fluoro-6-(5-(3-(3-fluoroazetidin-1-yl)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00901]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 581** (0.12 g, 0.16 mmol), $Pd(PPh_3)_2Cl_2$ (11.5 mg, 16 μmol), copper(I) iodide (3 mg, 16 μmol), triethylamine (0.23 mL, 1.64 mmol) and **Intermediate 642** (0.74 g, 1.64 mmol) in MeCN (6.5 mL) at 65 °C for 16 h. Conditions repeated. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) and catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (40 mg). LCMS (Method 15): 2.85 min, 766.4 $[M+H]^+$.

**Intermediate 744:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-2$^4$-fluoro-6-(5-(3-(3-fluoroazetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00902]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 743** (40 mg, 0.03 mmol) and 10% palladium on carbon (2.8 mg) in ethanol (2 mL) under a hydrogen atmosphere at RT for 6 h, to provide the title compound (17 mg). LCMS (Method 15): 2.87 min, 770.3 $[M+H]^+$.

**Intermediate 745:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00903]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 638** (1.75 g, 2.70 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.72 g, 2.97 mmol, CAS 109919-32-6) and $K_2CO_3$ (1.12 g, 8.11 mmol) in MeCN (35 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica gel, 0-60% EtOAc in petroleum ether) to provide the title compound (1.03 g). LCMS (Method 15): 2.88 min, 793.1 $[M+H]^+$.

**Intermediate 746:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00904]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 745** (1.03 g, 1.30 mmol) in DCE (0.64 L) and Grubbs II (0.11 g, 0.13 mmol) at 50 °C for 1 h. Purified by flash chromatography (24 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.78 g). LCMS (Method 15): 2.83 min, 765.1 $[M+H]^+$.

**Intermediate 747:** Ethyl 2-((3*S*,6*S*)-6-(5-((*E*)-2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00905]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 746** (0.27 g, 0.35 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (0.15 g, 0.74 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (26 mg, 35 µmol) and $Na_2CO_3$ (74 mg, 0.70 mmol) in 1,4-dioxane (4.8 mL) and water (1.6 mL) at 85 °C for 5 h. Conditions repeated. Purified by flash chromatography (12 g silica gel, eluting 0-20% EtOAc in petroleum ether), to provide the title compound (0.16 g). LCMS (Method 15): 2.85 min, 755.3 $[M+H]^+$.

**Intermediate 748:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00906]** A solution of **Intermediate 747** (0.16 g, 0.21 mmol) in DCM (4.6 mL) and TFA (0.32 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure then dissolved in DCM (16 mL). Azetidine (17 µL, 0.25 mmol), triethylamine (58 µL, 0.41 mmol) and 4 Å molecular sieves were added and stirred at RT for 20 min. STAB (88 mg, 0.41 mmol) was added and stirred at RT for 60 h. The mixture was filtered and filtrate concentrated under reduced pressure and purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (92 mg). LCMS (Method 15): 2.77 min, 768.3 $[M+H]^+$.

**Intermediate 749:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00907]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 748** (92 mg, 0.12 mmol) and 10% palladium on carbon (13 mg) in ethanol (12 mL) under a hydrogen atmosphere at RT for 6 h, to provide the title compound (85 mg). LCMS (Method 15): 2.81 min, 770.3 $[M+H]^+$.

**Intermediate 750:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[00908]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 638** (0.59 g, 0.82 mmol), **Intermediate 428** (0.24 g, 0.90 mmol) and $K_2CO_3$ (0.34 g, 2.45 mmol) in MeCN (10 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica gel, 20-60% EtOAc in petroleum ether) to provide the title compound (0.24 g). LCMS (Method 22): 2.32 min, 812.4 $[M+H]^+$.

**Intermediate 751:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00909]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 750** (0.24 g, 0.26 mmol) in DCE (0.13 L) and Grubbs II (22 mg, 26 µmol) at 50 °C for 4 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.18 g). LCMS (Method 21): 6.16 min, 784.3 $[M+H]^+$.

**Intermediate 752:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00910]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 751** (0.18 g, 0.18 mmol) and 10% palladium on carbon (19 mg) in ethanol (9 mL) under a hydrogen atmosphere at RT for 6 h. Purified by flash chromatography (12 g silica gel, eluting 5-10% MeOH in DCM) to provide the title compound (0.15 g). LCMS (Method 21): 6.22 min, 786.3 $[M+H]^+$.

**Intermediate 753:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00911]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 746** (0.22 g, 0.29 mmol), $Pd(PPh_3)_2Cl_2$ (14 mg, 20 µmol), copper(I) iodide (3.9 mg, 20 µmol), triethylamine (0.29 mL, 2.04 mmol) and *N*,*N*-dimethylpropargylamine (0.22 mL, 2.04 mmol, CAS 7223-38-3) in MeCN (3 mL) at 80 °C for 24 h. Conditions repeated. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.21 g). LCMS (Method 15): 2.75 min, 766.3 $[M+H]^+$.

**Intermediate 754:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00912]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 753** (0.21 g, 0.27 mmol) and 10% palladium on carbon (29 mg) in ethanol (27 mL) under a hydrogen atmosphere at RT for 6 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (76 mg). LCMS (Method 15): 2.85 min, 772.3 $[M+H]^+$.

**Intermediate 755:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00913]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 587** (0.61 g, 0.82 mmol), $Pd(PPh_3)_2Cl_2$ (58 mg, 82 µmol), copper(I) iodide (32 mg, 0.17 mmol), triethylamine (1.15 mL, 8.24 mmol) and *tert*-butyldimethyl(2-propynyloxy)silane (1.67 mL, 8.24 mmol, CAS 76782-82-6) in MeCN (6.5 mL) at 110 °C under microwave irradiation for 5 h. Conditions repeated for 2.5 h. Purified by flash chromatography (25 g silica gel, eluting 0-50% EtOAc in petroleum ether) then by reverse phase chromatography (38 g C18, 50-100% MeCN in 0.1% aqueous ammonia) to provide the title compound (0.72 g). LCMS (Method 28): 4.34 min, 827.7 $[M+H]^+$.

**Intermediate 756:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00914]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 755** (0.35 g, 0.37 mmol) and 10% palladium on carbon (39 mg) in ethanol (6 mL) under a hydrogen atmosphere at RT for 1.5 h, to provide the title compound (0.32 g). LCMS (Method 25): 4.16 min, 829.6 $[M-H]^-$.

**Intermediate 757:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-6-(5-(3-hydroxypropyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00915]** To a solution of **Intermediate 756** (0.32 g, 0.33 mmol) in THF (5 mL) was added TBAF (1 M in THF, 0.99 mL, 0.99 mmol) at 0 °C then stirred at RT for 2 h. The mixture was diluted with water and extracted with EtOAc. The organics were washed with water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure, then purified by flash chromatography (12 g silica gel, eluting 0-75% EtOAc in petroleum ether) to provide the title compound (0.18 g). LCMS (Method 25): 2.63 min, 717.2 $[M+H]^+$.

**Intermediate 758:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00916]** To a solution of **Intermediate 757** (0.16 g, 0.22 mmol) in DCM (3 mL) was added carbon tetrabromide (0.14 g, 0.44 mmol) and triphenylphosphine (0.11 g, 0.44 mmol) then stirred at RT for 2 h. The mixture was concentrated under reduced pressure. The residue was dissolved in MeCN (3 mL) then azetidine (73 µL, 1.09 mmol) and $K_2CO_3$ were added and stirred at RT for 2 h. The mixture was used directly in catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.13 g). LCMS (Method 25): 2.92 min, 756.3 $[M+H]^+$.

**Intermediate 759:** 5-Fluoro-2-iodo-3-methylphenol

**[00917]** To a suspension of sodium hydride (60% dispersion in oil, 8.0 g, 0.20 mol) in toluene (0.10 L) at 0 °C was added a solution of 3-fluoro-5-methylphenol (12.5 g, 99.1 mmol, CAS 216976-31-7) in toluene (50 mL) and stirred at 0 °C for 30 min. A solution of iodine (25.2 g, 99.3 mmol) in toluene (0.45 L) was added over 70 mins at 0 °C then stirred at RT for 30 min. The mixture was acidified to pH 5 with 2 M aqueous HCl then extracted with EtOAc. The organics were washed with water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (120 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (12.5 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 6.64 – 6.59 (m, 2H), 5.53 (d, 1H), 2.43 (s, 3H).

**Intermediate 760:** 5-Fluoro-2-iodo-1-(methoxymethoxy)-3-methylbenzene

**[00918]** To a solution of **Intermediate 759** (4.24 g, 16.8 mmol) in DCM (73 mL) at RT was added DIPEA (7.33 mL, 42.0 mmol) and chloromethyl methyl ether (2.03 g, 1.92 mmol) then stirred at RT for 18 h. The mixture was washed with water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure, to provide the title compound (5.3 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 6.72 – 6.68 (m, 2H), 5.22 (s, 2H), 3.51 (s, 3H), 2.46 (s, 3H).

**Intermediate 761:** 2-(4-Fluoro-2-(methoxymethoxy)-6-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

**[00919]** Prepared in an analogous manner to **Intermediate 2** using **Intermediate 760** (2.65 g, 8.95 mmol), bis(pinacolato)diboron (2.73 g, 10.7 mmol), $Cs_2CO_3$ (4.37 g, 13.4 mmol), tris(4-methoxyphenyl)phosphine (0.17 g, 0.49 mmol) and palladium acetate (0.10 g, 0.45 mmol) in EtOAc (90 mL) at 80 °C for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-10% EtOAc in petroleum ether) to provide the title compound (2.59 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 6.58 (dd, 1H), 6.52 (dd, 1H), 5.11 (s, 2H), 3.46 (s, 3H), 2.34 (s, 3H), 1.38 (s, 12H).

**Intermediate 762:** Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-2,4,4'-trifluoro-2'-(methoxymethoxy)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00920]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 761** (0.99 g, 3.35 mmol), **Intermediate 312** (1.0 g, 2.23 mmol), $K_3PO_4$ (1.42 g, 6.69 mmol) and XPhosPdG2 (0.18 g, 0.22 mmol) in 1,4-dioxane (41 mL), and water (10 mL) at 110 °C for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.94 g). LCMS (Method 22): 2.00 min, 536.2 $[M-H]^-$.

**Intermediate 763:** Ethyl (3*S*)-3-amino-3-(5-cyclopropyl-2,4,4'-trifluoro-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00921]** A suspension of **Intermediate 762** (1.50 g, 2.57 mmol) in 4 M HCl in 1,4-dioxane (6.4 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (1.23 g). LCMS (Method 22): 1.59 min, 394.1 $[M+H]^+$.

**Intermediate 764:** Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-2,4,4'-trifluoro-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00922]** To a stirred suspension of **Intermediate 763** (1.35 g, 3.42 mmol) and Boc anhydride (0.90 g, 4.11 mmol) in DCM (14 mL) was added DIPEA (0.89 mL, 5.13 mmol) and the mixture stirred for 16 h at RT. The reaction mixture was washed with 1 M aqueous HCl, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (24 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (1.44 g). LCMS (Method 22): 1.85 min, 394.1 $[M-Boc+H]^+$.

**Intermediate 765:** Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-2,4,4'-trifluoro-2'-methyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00923]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 764** (0.85 g, 1.64 mmol), phenyl triflimide (0.58 g, 1.64 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (0.64 g, 1.96 mmol) in DCM (8 mL) at RT for 20 h. Purified by flash chromatography (25 g silica gel, eluting 0–20% EtOAc in petroleum ether) to provide the title compound (0.93 g). LCMS (Method 15): 2.67 min, 624.2 $[M-H]^-$.

**Intermediate 766:** Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-2,4,4'-trifluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00924]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 765** (0.84 g, 1.29 mmol), 5-hexenylboronic acid (0.41 g, 3.23 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.45 g, 3.23 mmol), RuPhosPdG3 (0.11 g, 0.13 mmol) and RuPhos (60 mg, 0.13 mmol) in toluene (13 mL) and water (3 mL) at 95 °C for 1.5 h. Purified by flash chromatography (40 g silica gel, eluting 0-10% EtOAc in petroleum ether) to provide the title compound (1.10 g). LCMS (Method 15): 2.84 min, 558.3 $[M-H]^-$.

**Intermediate 767:** Ethyl (3*S*)-3-amino-3-(5-cyclopropyl-2,4,4'-trifluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00925]** A suspension of **Intermediate 766** (1.10 g, 1.47 mmol) in 4 M HCl in 1,4-dioxane (3.7 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure and purified by catch and release chromatography (10 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.72 g). LCMS (Method 15): 2.68 min, 460.1 $[M+H]^+$.

**Intermediate 768:** Ethyl (3*S*)-3-(5-cyclopropyl-2,4,4'-trifluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00926]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 767** (0.80 g, 1.50 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.27 g, 2.25 mmol, CAS 413622-10-3), DIPEA (0.78 mL, 4.50 mmol), HOBt (0.22 g, 1.65 mmol) and EDCI (0.35 g, 2.25 mmol) in MeCN (12 mL) at RT for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.78 g). LCMS (Method 15): 2.65 min, 558.2 $[M+H]^+$.

**Intermediate 769:** Ethyl (3*S*)-3-(5-cyclopropyl-2,4,4'-trifluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00927]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 768** (0.78 g, 1.39 mmol), triethylamine (0.39 mL, 2.77 mmol) and methanesulfonyl chloride (0.16 mL, 2.08 mmol) in DCM (18 mL) at RT for 2.5 h, to provide the title compound (0.88 g). LCMS (Method 15): 2.70 min, 636.3 $[M+H]^+$.

**Intermediate 770:** Ethyl (3*S*)-3-(5-cyclopropyl-2,4,4'-trifluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00928]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 769** (0.88 g, 1.29 mmol), **Intermediate 258** (0.30 g, 1.29 mmol) and $K_2CO_3$ (0.53 g, 3.87 mmol) in MeCN (21 mL) at reflux for 24 h. Additional **Intermediate 258** (32 mg, 0.14 mmol) and $K_2CO_3$ (54 mg, 0.39 mmol) were added and stirred at reflux for 4.5 h. Purified by flash chromatography (40 g silica gel, 0-3% (0.5% ammonia MeOH) in DCM) and reverse phase chromatography (38 g C18, 40-50% MeCN in 0.1% aqueous formic acid) to provide the title compound (0.31 g). LCMS (Method 15): 2.84 min, 774.3 $[M+H]^+$.

**Intermediate 771:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^2$,2$^4$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00929]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 770** (0.31 g, 0.37 mmol) in DCE (0.20 L) and Grubbs II (34 mg, 40 μmol) at 50 °C for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-3% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.27 g). LCMS (Method 15): 2.72 min, 746.3 $[M+H]^+$.

**Intermediate 772:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^2$,$2^4$-trifluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00930]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 771** (0.27 g, 0.24 mmol) and 10% palladium on carbon (25 mg) in ethanol (2.4 mL) under a hydrogen atmosphere at RT for 5 h. Purified by flash chromatography (12 g silica gel, eluting 0-3% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.24 g). LCMS (Method 15): 2.78 min, 748.3 $[M+H]^+$.

**Intermediate 773:** 4,4'-Difluoro-2'-hydroxy-5,6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde

**[00931]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 759** (5.0 g, 17.4 mmol), 2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (4.80 g, 17.4 mmol, CAS 2121513-83-3), $K_3PO_4$ (7.41 g, 34.9 mmol), palladium acetate (0.39 g, 1.75 mmol) and tricyclohexyl phosphine (0.49 g, 1.75 mmol) in toluene (80 mL) and water (11 mL) at 100 °C for 6 h. Purified by flash chromatography (40 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (2.89 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 10.36 (s, 1H), 7.57 (d, 1H), 7.36 (d, 1H), 6.61 – 6.50 (m, 2H), 5.13 (s, 1H), 2.39 (d, 3H), 2.02 (s, 3H).

**Intermediate 774:** 4,4'-Difluoro-3'-formyl-5',6-dimethyl-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate

**[00932]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 773** (3.34 g, 12.7 mmol), phenyl triflimide (4.55 g, 12.7 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (4.98 g, 15.3 mmol) in DCM (51 mL) at RT for 2 h. Purified by flash chromatography (80 g silica gel, eluting 0–15% EtOAc in petroleum ether) to provide the title compound (4.43 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 10.40 (s, 1H), 7.55 (dd, 1H), 7.33 (dd, 1H), 7.07 (dd, 1H), 6.98 (dd, 1H), 2.39 (d, 3H), 2.15 (s, 3H).

**Intermediate 775:** 4,4'-Difluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde

**[00933]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 774** (2.23 g, 5.66 mmol), 5-hexenylboronic acid (1.09 g, 8.48 mmol, CAS 1072952-16-9), $K_2CO_3$ (2.35 g, 17.0 mmol), palladium acetate (0.13 g, 0.57 mmol) and RuPhos (0.46 g, 0.85 mmol) in toluene (51 mL) and water (6 mL) at 100 °C for 2 h. Purified by flash chromatography (40 g

silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (1.0 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 10.41 (s, 1H), 7.45 (dd, 1H), 7.22 (dd, 1H), 6.83 – 6.78 (m, 2H), 5.74 – 5.63 (m, 1H), 4.94 – 4.87 (m, 2H), 2.38 (d, 3H), 2.28 – 2.24 (m, 2H), 1.97 (s, 3H), 1.91 (q, 2H), 1.42 – 1.35 (m, 2H), 1.28 – 1.22 (m, 2H).

**Intermediate 776:** (*R*,*Z*)-*N*-((4,4'-Difluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)methylene)-2-methylpropane-2-sulfinamide

**[00934]** Prepared in an analogous manner to **Intermediate 102** using **Intermediate 775** (1.72 g, 5.24 mmol), (*R*)-2-methylpropane-2-sulfinimide (0.70 g, 5.76 mmol, CAS 196929-78-9) and titanium ethoxide (1.79 g, 7.85 mmol) in THF (30 mL) at 40 °C for 2 h, to provide the title compound (2.26 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 8.94 (s, 1H), 7.58 – 7.53 (m, 1H), 7.10 (dd, 1H), 6.82 (dd, 2H), 5.75 – 5.61 (m, 1H), 4.94 – 4.85 (m, 2H), 2.36 (d, 3H), 2.33 – 2.26 (m, 2H), 2.00 (s, 3H), 1.91 (t, 2H), 1.45 – 1.39 (m, 2H), 1.27 – 1.23 (m, 11H).

**Intermediate 777:** Ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00935]** Prepared in an analogous manner to **Intermediate 104** using zinc (1.71 g, 26.2 mmol), chlorotrimethylsilane (0.13 mL, 1.05 mmol) and ethyl bromoacetate (1.45 mL, 13.1 mmol) in THF (32 mL) at 65 °C for 1 h, then **Intermediate 776** (2.26 g, 5.24 mmol) in THF (19 mL) at RT for 2 h. Purified by flash chromatography (40 g silica gel, eluting 0-80% EtOAc in petroleum ether) to provide the title compound (1.86 g). LCMS (Method 15): 2.78 min, 520.2 $[M+H]^+$.

**Intermediate 778:** Ethyl (*S*)-3-amino-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00936]** A suspension of **Intermediate 777** (1.86 g, 3.58 mmol) in 4 M HCl in 1,4-dioxane (18 mL) was stirred at RT for 1 h. The mixture was diluted with water and washed with EtOAc. The aqueous was basified with aqueous $NaHCO_3$ and extracted with EtOAc. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure, to provide the title compound (1.47 g). LCMS (Method 15): 2.67 min, 416.2 $[M+H]^+$.

**Intermediate 779:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00937]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 778** (1.48 g, 3.56 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.64 g, 5.34 mmol, CAS 413622-10-3), DIPEA (1.86 mL, 10.7 mmol), HOBt (0.53 g, 3.92 mmol) and EDCI (0.83 g, 5.34 mmol) in MeCN (36 mL) at RT for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-60%

EtOAc in petroleum ether) to provide the title compound (1.30 g). LCMS (Method 15): 2.62 min, 514.2 $[M+H]^+$.

**Intermediate 780:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00938]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 779** (0.85 g, 1.66 mmol), triethylamine (0.46 mL, 3.31 mmol) and methanesulfonyl chloride (0.19 mL, 2.48 mmol) in DCM (17 mL) at RT for 1 h, to provide the title compound (0.96 g). LCMS (Method 15): 2.67 min, 592.2 $[M+H]^+$.

**Intermediate 781:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00939]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 780** (0.43 g, 0.68 mmol), **Intermediate 258** (0.18 g, 0.75 mmol) and $K_2CO_3$ (0.28 g, 2.05 mmol) in MeCN (9 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, 0-8% MeOH in DCM) to provide the title compound (0.40 g). LCMS (Method 15): 2.83 min, 730.3 $[M+H]^+$.

**Intermediate 782:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00940]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 781** (0.40 g, 0.40 mmol) in DCE (0.26 L) and Grubbs II (34 mg, 40 μmol) at 50 °C for 2 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.36 g). LCMS (Method 15): 2.73 min, 702.3 $[M+H]^+$.

**Intermediate 783:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00941]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 782** (0.36 g, 0.35 mmol) and 10% palladium on carbon (37 mg) in ethanol (6.2 mL) under a hydrogen atmosphere at RT for 6 h. Purified by flash chromatography (12 g silica gel, eluting 5-10% MeOH in DCM) to provide the title compound (0.30 g). LCMS (Method 15): 2.76 min, 704.3 $[M+H]^+$.

**Intermediate 784:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00942]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 780** (0.51 g, 0.86 mmol), **Intermediate 428** (0.25 g, 0.95 mmol) and $K_2CO_3$ (0.38 g, 2.59 mmol) in MeCN (10 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, 0-8% MeOH in DCM) to provide the title compound (0.24 g). LCMS (Method 15): 2.83 min, 758.4 $[M+H]^+$.

**Intermediate 785:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00943]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 784** (0.30 g, 0.35 mmol) in DCE (0.20 L) and Grubbs II (30 mg, 35 µmol) at 50 °C for 2 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.15 g). LCMS (Method 15): 2.92 min, 730.3 $[M+H]^+$.

**Intermediate 786:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00944]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 785** (0.15 g, 0.17 mmol) and 10% palladium on carbon (18 mg) in ethanol (4.4 mL) under a hydrogen atmosphere at RT for 6 h. Purified by flash chromatography (4 g silica gel, eluting 5-10% MeOH in DCM) to provide the title compound (0.16 g). LCMS (Method 15): 2.96 min, 732.4 $[M+H]^+$.

**Intermediate 787:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[00945]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 780** (0.53 g, 0.86 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.23 g, 0.94 mmol, CAS 109919-32-6) and $K_2CO_3$ (0.36 g, 2.57 mmol) in MeCN (11 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, 0-40% EtOAc in petroleum ether) to provide the title compound (0.34 g). LCMS (Method 15): 2.88 min, 739.2 $[M+H]^+$.

**Intermediate 788:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00946]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 787** (0.34 g, 0.47 mmol) in DCE (0.19 L) and Grubbs II (39 mg, 46 µmol) at 50 °C for 2.5 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.35 g). LCMS (Method 15): 2.80 min, 709.1 $[M+H]^+$.

**Intermediate 789:** Ethyl 2-((3*S*,6*S*)-6-(5-((*E*)-2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00947]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 788** (0.35 g, 0.49 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (0.10 g, 0.51 mmol, CAS 1201905-61-4), Pd(dppf)$Cl_2$ (36 mg, 49 µmol) and $Na_2CO_3$ (0.10 g, 0.98 mmol) in 1,4-dioxane (4.2 mL) and water (1.4 mL) at 85 °C for 1 h. Purified by flash chromatography (40 g silica gel, eluting 0-100% EtOAc in petroleum ether), to provide the title compound (0.23 g). LCMS (Method 15): 2.83 min, 701.3 $[M+H]^+$.

**Intermediate 790:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-6-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00948]** A solution of **Intermediate 789** (0.23 g, 0.32 mmol) in DCM (6.4 mL) and TFA (5.4 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.29 g). LCMS (Method 12): 2.61 min, 673.2 $[M+H]^+$.

**Intermediate 791:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00949]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 790** (0.30 g, 0.27 mmol), azetidine (21 µL, 0.32 mmol), triethylamine (0.11 mL, 0.80 mmol) in DCM (9 mL) and 4 Å molecular sieves at RT for 1.5 h, then STAB (0.11 g, 0.53 mmol) at RT for 16 h. Purified by flash chromatography (12 g silica, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (98 mg). LCMS (Method 15): 2.75 min, 714.3 $[M+H]^+$.

**Intermediate 792:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00950]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 791** (98 mg, 0.11 mmol) and 10% palladium on carbon (12 mg) in ethanol (3.6 mL) under a hydrogen atmosphere at RT for 6 h. Purified by flash chromatography (4 g silica gel, eluting 5-10% MeOH in DCM) to provide the title compound (78 mg). LCMS (Method 15): 2.80 min, 716.3 $[M+H]^+$.

**Intermediate 793**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-chloro-5-cyclopropyl-4-fluoro-6'-hydroxy-[1,1'-biphenyl]-3-yl)propanoate

**[00951]** Prepared in an analogous manner to **Intermediate 3** using 2-bromo-3-chlorophenol (2.26 g, 10.9 mmol, CAS 855836-62-3), **Intermediate 377** (4.0 g, 8.38 mmol), $K_3PO_4$ (3.56 g, 16.8 mmol), palladium acetate (0.19 g, 0.84 mmol) and tricyclohexyl phosphine (0.23 g, 0.84 mmol) in toluene (60 mL) and water (10 mL) at 100 °C for 3 h. Purified by flash chromatography (80 g silica gel, eluting 0-25% EtOAc in petroleum ether) to provide the title compound (3.25 g). LCMS (Method 15): 2.35 min, 378.1 $[M\text{-}Boc+H]^+$.

**Intermediate 794:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-chloro-5-cyclopropyl-4-fluoro-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00952]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 793** (3.25 g, 5.43 mmol), phenyl triflimide (2.33 g, 6.52 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (2.12 g, 6.52 mmol) in DCM (70 mL) at RT for 2 h. Purified by flash chromatography (80 g silica gel, eluting 0–30% EtOAc in petroleum ether) to provide the title compound (3.07 g). LCMS (Method 15): 2.66 min, 510.0 $[M\text{-}Boc+H]^+$.

**Intermediate 795:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-chloro-5-cyclopropyl-4-fluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)propanoate

**[00953]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 794** (2.17 g, 3.34 mmol), 5-hexenylboronic acid (0.43 g, 3.34 mmol, CAS 1072952-16-9), $K_2CO_3$ (1.39 g, 10.0 mmol), palladium acetate (75 mg, 0.33 mmol) and RuPhos (0.23 g, 0.50 mmol) in toluene (21 mL) and water (3 mL) at 100 °C for 2.5 h. Purified by flash chromatography (40 g silica gel, eluting 5-20% EtOAc in petroleum ether) to provide the title compound (1.39 g). LCMS (Method 15): 2.89 min, 444.1 $[M\text{-}Boc+H]^+$.

**Intermediate 796:** Ethyl (*S*)-3-amino-3-(2'-chloro-5-cyclopropyl-4-fluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00954]** A suspension of **Intermediate 795** (1.80 g, 3.31 mmol) in 4 M HCl in 1,4-dioxane (8.3 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure, to provide the title compound (1.73 g). LCMS (Method 15): 2.70 min, 444.1 $[M+H]^+$.

**Intermediate 797:** Ethyl (*S*)-3-(2'-chloro-5-cyclopropyl-4-fluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00955]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 796** (1.73 g, 3.13 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.56 g, 4.79 mmol, CAS 413622-10-3), DIPEA (1.67 mL, 9.40 mmol), HOBt (0.42 g, 3.13 mmol) and EDCI (0.72 g, 3.75 mmol) in MeCN (18 mL) at RT for 20 h. Purified by flash chromatography (40 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (1.30 g). LCMS (Method 15): 2.64 min, 542.2 $[M+H]^+$.

**Intermediate 798:** Ethyl (*S*)-3-(2'-chloro-5-cyclopropyl-4-fluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00956]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 797** (0.42 g, 0.61 mmol), triethylamine (0.17 mL, 1.22 mmol) and methanesulfonyl chloride (71 µL, 0.91 mmol) in DCM (4.3 mL) at RT for 1 h, to provide the title compound (0.47 g). LCMS (Method 15): 2.70 min, 620.2 $[M+H]^+$.

**Intermediate 799:** Ethyl (*S*)-3-(2'-chloro-5-cyclopropyl-4-fluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00957]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 798** (0.47 g, 0.53 mmol), **Intermediate 258** (0.14 g, 0.59 mmol) and $K_2CO_3$ (0.22 g, 1.60 mmol) in MeCN (7 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, 3-8% (5% ammonia MeOH) in DCM) to provide the title compound (0.15 g). LCMS (Method 15): 2.86 min, 758.3 $[M+H]^+$.

**Intermediate 800:** Ethyl 2-((3*S*,6*S*)-$1^6$-chloro-$2^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00958]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 799** (0.12 g, 0.15 mmol) in DCE (74 mL) and Grubbs II (13 mg, 15 µmol) at 50 °C for 4 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% (5% ammonia MeOH) in DCM) to provide the title compound (0.10 g). LCMS (Method 15): 2.74 min, 730.3 $[M+H]^+$.

**Intermediate 801:** Ethyl 2-((3*S*,6*S*)-$1^6$-chloro-$2^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00959]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 800** (0.10 g, 0.11 mmol) and 10% palladium on carbon (12 mg) in EtOAc (5.4 mL) under a hydrogen atmosphere at RT for 3.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% (5% ammonia MeOH) in DCM) to provide the title compound (91 mg). LCMS (Method 15): 2.78 min, 732.3 $[M+H]^+$.

**Intermediate 802**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4'-fluoro-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00960]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 759** (0.84 g, 2.83 mmol), **Intermediate 666** (2.03 g, 4.42 mmol), $K_3PO_4$ (1.20 g, 5.66 mmol), XPhosPdG2 (0.15 g, 0.19 mmol) in toluene (34 mL) and water (8.6 mL) at 100 °C for 1 h. Purified by flash

chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.57 g). LCMS (Method 22): 2.37 min, 456.3 $[M-H]^-$.

**Intermediate 803:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4'-fluoro-2'-methyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00961]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 802** (0.86 g, 1.88 mmol), phenyl triflimide (0.81 g, 2.26 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (0.74 g, 2.26 mmol) in DCM (20 mL) at RT for 2 h. Purified by flash chromatography (24 g silica gel, eluting 0–40% EtOAc in petroleum ether) to provide the title compound (0.82 g). LCMS (Method 22): 2.67 min, 588.2 $[M-H]^-$.

**Intermediate 804:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4'-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00962]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 803** (0.72 g, 1.21 mmol), 5-hexenylboronic acid (0.39 g, 3.03 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.42 g, 3.03 mmol), RuPhosPdG3 (0.15 g, 0.18 mmol) and RuPhos (57 g, 0.12 mmol) in toluene (10 mL) and water (2.5 mL) at 100 °C for 1.5 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.53 g). LCMS (Method 15): 2.92 min, 424.2 $[M-Boc+H]^+$.

**Intermediate 805:** Ethyl (*S*)-3-amino-3-(5-cyclopropyl-4'-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00963]** A suspension of **Intermediate 804** (0.58 g, 1.11 mmol) in 4 M HCl in 1,4-dioxane (10 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure, to provide the title compound (0.51 g). LCMS (Method 15): 2.72 min, 424.1 $[M+H]^+$.

**Intermediate 806:** Ethyl (*S*)-3-(5-cyclopropyl-4'-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[00964]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 805** (0.51 g, 1.11 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.21 g, 1.77 mmol, CAS 413622-10-3), DIPEA (0.59 mL, 3.39 mmol), HOBt (0.15 g, 1.11 mmol) and EDCI (0.25 g, 1.33 mmol) in MeCN (9 mL) at RT for 18 h. Purified by flash chromatography (24 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.41 g). LCMS (Method 15): 2.67 min, 522.2 $[M+H]^+$.

**Intermediate 807:** Ethyl (*S*)-3-(5-cyclopropyl-4'-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[00965]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 806** (0.41 g, 0.78 mmol), triethylamine (0.22 mL, 1.56 mmol) and methanesulfonyl chloride (90 µL, 1.17 mmol) in DCM (8 mL) at RT for 1 h, to provide the title compound (0.51 g). LCMS (Method 15): 2.72 min, 600.2 $[M+H]^+$.

**Intermediate 808:** Ethyl (*S*)-3-(5-cyclopropyl-4'-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00966]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 807** (0.47 g, 0.78 mmol), **Intermediate 258** (0.18 g, 0.78 mmol) and $K_2CO_3$ (0.32 g, 2.34 mmol) in MeCN (10 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, 0-3% (5% ammonia MeOH) in DCM) to provide the title compound (0.15 g). LCMS (Method 15): 2.88 min, 738.4 $[M+H]^+$.

**Intermediate 809:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00967]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 808** (0.15 g, 0.21 mmol) in DCE (68 mL) and Grubbs II (18 mg, 21 µmol) at 50 °C for 4 h. Purified by flash chromatography (25 g silica gel, eluting 0-5% (5% ammonia MeOH) in DCM) to provide the title compound (0.12 g). LCMS (Method 15): 2.75 min, 710.3 $[M+H]^+$.

**Intermediate 810:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00968]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 809** (0.12 g, 0.04 mmol) and 10% palladium on carbon (4 mg) in EtOAc (4 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-5% (5% ammonia MeOH) in DCM) to provide the title compound (0.11 g). LCMS (Method 15): 2.79 min, 712.3 $[M+H]^+$.

**Intermediate 811:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-((tert-butyldimethylsilyl)oxy)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00969]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 746** (0.29 g, 0.38 mmol), $Pd(PPh_3)_2Cl_2$ (27 mg, 38 µmol), copper(I) iodide (14.5 mg, 76 µmol), triethylamine (0.53 mL, 3.80 mmol) and *tert*-butyldimethyl-prop-2-ynoxy-silane (0.77 mL, 3.80 mmol, CAS 76782-82-6) in DMF (3 mL) at 110 °C for 5 h. Purified by flash chromatography

(25 g silica gel, eluting 0-15% EtOAc in petroleum ether) to provide the title compound (0.21 g). LCMS (Method 28): 4.25 min, 853.5 $[M+H]^+$.

**Intermediate 812:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-((tert-butyldimethylsilyl)oxy)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00970]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 811** (0.20 g, 0.24 mmol) and 10% palladium on carbon (25 mg) in ethanol (15 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.13 g). LCMS (Method 28): 4.43 min, 859.6 $[M+H]^+$.

**Intermediate 813:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(5-(3-hydroxypropyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00971]** Prepared in an analogous manner to **Intermediate 757** using **Intermediate 812** (0.13 g, 0.11 mmol) and TBAF (1 M in THF, 0.32 mL, 0.32 mmol) in THF (2 mL) at RT for 7 h. Purified by flash chromatography (12 g silica gel, eluting 0-75% EtOAc in petroleum ether) to provide the title compound (71 mg). LCMS (Method 28): 3.31 min, 745.7 $[M+H]^+$.

**Intermediate 814:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00972]** Prepared in an analogous manner to **Intermediate 758** using **Intermediate 813** (71 mg, 95 μmol), triphenylphosphine (50 mg, 0.19 mmol), carbon tetrabromide (63 mg, 0.19 mmol) in DCM (1.3 mL) at RT for 2 h. Additional triphenylphosphine (50 mg, 0.19 mmol) and carbon tetrabromide (63 mg, 0.19 mmol) added and stirred at RT for 2 h. Then azetidine (64 μL, 0.95 mmol) and $K_2CO_3$ (26 mg, 0.19 mmol) in MeCN (1.3 mL) at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) then by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (45 mg). LCMS (Method 15): 3.01 min, 784.3 $[M+H]^+$.

**Intermediate 815:** (*E*)-4-(Difluoromethyl)-5-(2-ethoxyvinyl)-2-methoxypyridine

**[00973]** Prepared in an analogous manner to **Intermediate 364** using 5-bromo-4-(difluoromethyl)-2-methoxypyridine (0.79 g, 3.30 mmol, CAS 1806764-22-6), *trans*-2-ethoxyvinylboronic acid pinacol ester (0.72 g, 3.63 mmol, CAS 1201905-61-4), $Pd(PPh_3)_4$ (0.19 g, 0.17 mmol) and $K_2CO_3$ (1.40 g, 9.91 mmol) in 1,4-dioxane (9 mL) and water (1.8 mL) at 100 °C for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-30% EtOAc in

petroleum ether), to provide the title compound (0.60 g). $^1$H NMR (500 MHz; $CDCl_3$) δ: 8.12 (s, 1H), 6.90 (s, 1H), 6.76 – 6.49 (m, 2H), 5.82 (d, 1H), 3.93 (d, 5H), 1.36 (t, 3H).

**Intermediate 816:** 2-(4-(Difluoromethyl)-6-methoxypyridin-3-yl)-*N*,*N*-dimethylethan-1-amine

**[00974]** A solution of **Intermediate 815** (0.74 g, 3.21 mmol) in TFA (4 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure then dissolved in DCM (10 mL). Dimethylamine (2 M in THF, 3.2 mL, 3.2 mmol) and triethylamine (0.80 mL, 5.77 mmol) were added and stirred at RT for 1 h. Sodium borohydride (1.36 g, 6.41 mmol) was added and stirred at RT for 3 h. The mixture was filtered and filtrate concentrated under reduced pressure and purified by flash chromatography (25 g silica, eluting 0-20% (5% ammonia MeOH) in DCM) to provide the title compound (0.56 g). LCMS (Method 15): 1.65 min, 231.1 $[M+H]^+$.

**Intermediate 817:** 4-(Difluoromethyl)-5-(2-(dimethylamino)ethyl)pyridin-2(1*H*)-one

**[00975]** A solution of **Intermediate 816** (0.56 g, 2.42 mmol) in 33% HBr in AcOH (8.33 mL, 48.0 mmol) was stirred at 85 °C for 2 h. The mixture was cooled and concentrated under reduced pressure. Conditions repeated at 85 °C for 4 h. The crude product was purified by catch and release chromatography (10 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.55 g). LCMS (Method 15): 1.06 min, 217.0 $[M+H]^+$.

**Intermediate 818:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(4-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[00976]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 638** (0.49 g, 0.76 mmol), **Intermediate 817** (0.18 g, 0.84 mmol) and $K_2CO_3$ (0.32 g, 2.28 mmol) in MeCN (11 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica gel, 0-3% (1 M ammonia MeOH) in DCM) to provide the title compound (0.26 g). LCMS (Method 15): 2.78 min, 766.4 $[M+H]^+$.

**Intermediate 819:** Ethyl 2-((3*S*,6*S*)-6-(4-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00977]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 818** (0.24 g, 0.31 mmol) in DCE (0.15 L) and Grubbs II (27 mg, 31 μmol) at 50 °C for 1 h. Purified by flash chromatography (25 g silica gel, eluting 0-5% (5% ammonia MeOH) in DCM) to provide the title compound (0.22 g). LCMS (Method 15): 2.68 min, 738.3 $[M+H]^+$.

**Intermediate 820:** Ethyl 2-((3*S*,6*S*)-6-(4-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00978]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 819** (0.22 g, 0.29 mmol) and 10% palladium on carbon (31 mg) in ethanol (28 mL) under a hydrogen atmosphere at RT for 6 h, to provide the title compound (0.18 g). LCMS (Method 15): 2.71 min, 740.3 $[M+H]^+$.

**Intermediate 821:** 5-Fluoro-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

**[00979]** A suspension of **Intermediate 761** (9.13 g, 29.6 mmol) in 4 M HCl in 1,4-dioxane (37 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (8.16 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 8.75 (d, 1H), 6.43-6.39 (m, 2H), 2.47 (s, 3H), 1.36 (s, 12H).

**Intermediate 822:** Ethyl (*S*)-3-amino-3-(5-bromo-2,3-difluorophenyl)propanoate

**[00980]** A suspension of ethyl (3*S*)-3-(5-bromo-2,3-difluoro-phenyl)-3-[[(*R*)-*tert*-butylsulfinyl]amino]propanoate (13.5 g, 33.2 mmol, CAS 2640364-10-7) in 4 M HCl in 1,4-dioxane (40 mL) and ethanol (40 mL) was stirred at 70 °C for 17 h. The mixture concentrated under reduced pressure, diluted with water and washed with EtOAc. The aqueous was basified with aqueous $NaHCO_3$ and extracted with EtOAc. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure, to provide the title compound (8.10 g). LCMS (Method 15): 1.79 min, 307.8 $[M+H]^+$.

**Intermediate 823:** Ethyl (*S*)-3-(5-bromo-2,3-difluorophenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00981]** To a stirred suspension of **Intermediate 822** (8.0 g, 26.0 mmol) and Boc anhydride (6.80 g, 31.2 mmol) in DCM (0.10 L) was added DIPEA (7.0 mL, 40.2 mmol) and the mixture stirred for 16 h at RT. The reaction mixture was washed with 1 M aqueous HCl, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (80 g silica gel, eluting 0-10% EtOAc in petroleum ether) to provide the title compound (8.7 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.29 – 7.21 (m, 2H), 5.69 (br s, 1H), 5.30 (br s, 1H), 4.09 (q, 2H), 2.82 (d, 2H), 1.43 (s, 9H), 1.19 (t, 3H).

**Intermediate 824**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4,4',5-trifluoro-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00982]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 823** (1.0 g, 2.45 mmol), **Intermediate 821** (1.0 g, 3.70 mmol), $K_3PO_4$ (1.60 g, 7.54 mmol), XPhosPdG2 (0.20 g, 0.25 mmol) in toluene (20 mL) and water (4 mL) at 85 °C for 20 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.96 g). LCMS (Method 23): 2.19 min, 452.5 $[M-H]^-$.

**Intermediate 825:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4,4',5-trifluoro-2'-methyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00983]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 824** (0.96 g, 2.10 mmol), phenyl triflimide (0.75 g, 2.10 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (0.75 g, 2.30 mmol) in DCM (15 mL) at RT for 2 h. Purified by flash chromatography (25 g silica gel, eluting 0–20% EtOAc in petroleum ether) to provide the title compound (0.99 g). LCMS (Method 23): 2.47 min, 584.5 $[M-H]^-$.

**Intermediate 826:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4,4',5-trifluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00984]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 825** (0.86 g, 1.43 mmol), 5-hexenylboronic acid (0.28 g, 2.15 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.59 g, 4.30 mmol), palladium acetate (32 mg, 0.14 mmol) and RuPhos (0.10 g, 0.21 mmol) in toluene (10 mL) and water (2 mL) at 100 °C for 1 h. Purified by flash chromatography (40 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.65 g). LCMS (Method 23): 2.70 min, 420.3 $[M-Boc+H]^+$.

**Intermediate 827:** Ethyl (*S*)-3-amino-3-(4,4',5-trifluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00985]** A suspension of **Intermediate 826** (0.65 g, 1.25 mmol) in 4 M HCl in 1,4-dioxane (3 mL) was stirred at RT for 18 h. The mixture was concentrated under reduced pressure to provide the title compound (0.58 g). LCMS (Method 23): 1.90 min, 421.0 $[M+H]^+$.

**Intermediate 828:** Ethyl (*S*)-3-((*R*)-2-hydroxypent-4-enamido)-3-(4,4',5-trifluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00986]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 827** (0.58 g, 1.24 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.15 g, 1.25 mmol, CAS 413622-10-3), DIPEA (0.70 mL, 4.02 mmol), HOBt (0.21 g, 1.24 mmol) and EDCI (0.31 g, 1.62 mmol) in MeCN (10 mL) at RT for 18 h. Purified by flash chromatography (24 g silica gel, eluting 0-5% MeOH in DCM) to provide the title compound (0.54 g). LCMS (Method 23): 2.46 min, 518.4 $[M+H]^+$.

**Intermediate 829:** Ethyl (*S*)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)-3-(4,4',5-trifluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00987]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 828** (0.54 g, 1.04 mmol), triethylamine (0.70 mL, 5.02 mmol) and methanesulfonyl chloride (0.80 mL,

10.3 mmol) in DCM (10 mL) at RT for 1 h, to provide the title compound (0.62 g). LCMS (Method 7): 2.51 min, 594.6 $[M-H]^-$.

**Intermediate 830:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4,4',5-trifluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00988]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 829** (0.62 g, 1.04 mmol), **Intermediate 258** (0.25 g, 1.05 mmol) and $K_2CO_3$ (0.43 g, 3.12 mmol) in MeCN (10 mL) at reflux for 18 h. Purified by reverse phase chromatography (105 g C18, 0-40% MeCN in 0.1% aqueous formic acid) to provide the title compound (0.18 g). LCMS (Method 19): 5.79 min, 732.7 $[M-H]^-$.

**Intermediate 831:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$,$2^5$-trifluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[00989]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 830** (0.18 g, 0.22 mmol) in DCE (0.20 L) and Grubbs II (40 mg, 47 µmol) at 50 °C for 2 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.12 g). LCMS (Method 19): 5.51 min, 704.7 $[M-H]^-$.

**Intermediate 832:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$,$2^5$-trifluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[00990]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 831** (0.12 g, 0.13 mmol) and 10% palladium on carbon (50 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 2 h, to provide the title compound (61 mg). LCMS (Method 11): 2.64 min, 706.7 $[M-H]^-$.

**Intermediate 833:** Ethyl (*S*)-3-amino-3-(5-bromo-3-chloro-2-fluorophenyl)propanoate

**[00991]** A suspension of ethyl (3*S*)-3-(5-bromo-3-chloro-2-fluoro-phenyl)-3-[[(*R*)-*tert*-butylsulfinyl]amino]propanoate (3.3 g, 6.93 mmol, CAS 2640364-02-7) in 4 M HCl in 1,4-dioxane (20 mL) and ethanol (40 mL) was stirred at RT for 5 h. The mixture concentrated under reduced pressure, diluted with water and washed with EtOAc. The aqueous was basified with aqueous $NaHCO_3$ and extracted with EtOAc. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure, to provide the title compound (2.67 g). LCMS (Method 15): 1.93 min, 325.9 $[M+H]^+$.

**Intermediate 834:** Ethyl (*S*)-3-(5-bromo-3-chloro-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[00992]** To a stirred suspension of **Intermediate 833** (1.53 g, 4.34 mmol) and Boc anhydride (1.04 g, 4.77 mmol) in DCM (28 mL) was added triethylamine (0.91 mL, 6.51 mmol) and the mixture stirred at RT for 60 h. The reaction mixture concentrated under reduced pressure. The crude product was purified by flash chromatography (40 g silica gel, eluting 0-10% EtOAc in petroleum ether) to provide the title compound (1.39 g). LCMS (Method 15): 2.34 min, 424.0 $[M-H]^-$.

**Intermediate 835**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-chloro-4,4'-difluoro-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00993]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 834** (0.24 g, 0.52 mmol), **Intermediate 821** (0.20 g, 0.80 mmol), $K_3PO_4$ (0.33 g, 1.56 mmol), XPhosPdG2 (41 mg, 0.05 mmol) in 1,4-dioxane (9.4 mL) and water (2.4 mL) at 100 °C for 1 h. Purified by flash chromatography (25 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.20 g). LCMS (Method 15): 2.33 min, 468.2 $[M-H]^-$.

**Intermediate 836:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-chloro-4,4'-difluoro-2'-methyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[00994]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 835** (0.45 g, 0.70 mmol), phenyl triflimide (0.25 g, 0.70 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (0.27 g, 0.84 mmol) in DCM (3.5 mL) at RT for 20 h. Purified by flash chromatography (25 g silica gel, eluting 0–20% EtOAc in petroleum ether) to provide the title compound (0.40 g). LCMS (Method 25): 2.63 min, 600.1 $[M-H]^-$.

**Intermediate 837:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-chloro-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00995]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 836** (0.95 g, 1.34 mmol), 5-hexenylboronic acid (0.17 g, 1.34 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.56 g, 4.02 mmol), palladium acetate (30 mg, 0.13 mmol) and RuPhos (94 mg, 0.20 mmol) in toluene (8.4 mL) and water (1.2 mL) at 100 °C for 1 h. Purified by flash chromatography (120 g silica gel, eluting 0-10% EtOAc in petroleum ether) to provide the title compound (0.42 g). LCMS (Method 15): 2.87 min, 436.1 $[M\text{-Boc}+H]^+$.

**Intermediate 838:** Ethyl (*S*)-3-amino-3-(5-chloro-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[00996]** A suspension of **Intermediate 837** (0.53 g, 0.97 mmol) in 4 M HCl in 1,4-dioxane (2.5 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.57 g). LCMS (Method 15): 2.68 min, 436.2 $[M+H]^+$.

**Intermediate 839:** Ethyl (*S*)-3-((*R*)-2-hydroxypent-4-enamido)-3-(5-chloro-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00997]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 838** (0.57 g, 0.91 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.16 g, 1.36 mmol, CAS 413622-10-3), DIPEA (0.48 mL, 2.78 mmol), HOBt (0.12 g, 0.91 mmol) and EDCI (0.21 g, 1.09 mmol) in MeCN (9.1 mL) at RT for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.35 g). LCMS (Method 15): 2.66 min, 534.2 $[M+H]^+$.

**Intermediate 840:** Ethyl (*S*)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)-3-(5-chloro-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00998]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 839** (0.35 g, 0.63 mmol), triethylamine (0.18 mL, 1.27 mmol) and methanesulfonyl chloride (74 µL, 0.95 mmol) in DCM (8 mL) at RT for 2 h, to provide the title compound (0.41 g). LCMS (Method 15): 2.70 min, 612.2 $[M+H]^+$.

**Intermediate 841:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-chloro-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[00999]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 840** (0.41 g, 0.63 mmol), **Intermediate 258** (0.16 g, 0.69 mmol) and $K_2CO_3$ (0.30 g, 2.20 mmol) in MeCN (10 mL) at reflux for 18 h. Purified by reverse phase chromatography (105 g C18, 40-50% MeCN in 0.1% aqueous formic acid) to provide the title compound (0.24 g). LCMS (Method 15): 2.87 min, 750.3 $[M+H]^+$.

**Intermediate 842:** Ethyl 2-((3*S*,6*S*)-$2^5$-chloro-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001000]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 841** (0.21 g, 0.25 mmol) in DCE (0.13 L) and Grubbs II (23 mg, 27 µmol) at 50 °C for 7 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.13 g). LCMS (Method 15): 2.77 min, 722.3 $[M+H]^+$.

**Intermediate 843:** Ethyl 2-((3*S*,6*S*)-$2^5$-chloro-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001001]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 842** (0.13 g, 0.18 mmol) and 10% palladium on carbon (19 mg) in ethanol (1.8 mL) under a

hydrogen atmosphere at RT for 6 h, to provide the title compound (0.12 g). LCMS (Method 15): 2.81 min, 724.4 $[M+H]^+$.

**Intermediate 844:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-3-methyl-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001002]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 508** (0.63 g, 0.88 mmol), 5-bromo-3-methyl-1*H*-pyridin-2-one (0.25 g, 1.32 mmol, CAS 89488-30-2) and $K_2CO_3$ (0.36 g, 2.64 mmol) in MeCN (10 mL) at reflux for 18 h. Purified by flash chromatography (24 g silica gel, 0-35% EtOAc in petroleum ether) to provide the title compound (0.36 g). LCMS (Method 22): 2.87 min, 709.2 $[M+H]^+$.

**Intermediate 845:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-3-methyl-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001003]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 844** (0.36 g, 0.49 mmol) in DCE (0.24 L) and Grubbs II (41 mg, 49 µmol) at 50 °C for 1 h. Purified by flash chromatography (25 g silica gel, eluting 10-40% EtOAc in petroleum ether) to provide the title compound (0.25 g). LCMS (Method 15): 2.84 min, 681.2 $[M+H]^+$.

**Intermediate 846:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-((*E*)-2-ethoxyvinyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001004]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 845** (0.25 g, 0.31 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (64 mg, 0.32 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (25 mg, 31 µmol) and $Na_2CO_3$ (65 mg, 0.62 mmol) in 1,4-dioxane (7 mL) and water (1.9 mL) at 85 °C for 1 h. Purified by flash chromatography (40 g silica gel, eluting 0-100% EtOAc in petroleum ether), to provide the title compound (0.12 g). LCMS (Method 11): 2.81 min, 673.4 $[M+H]^+$.

**Intermediate 847:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-6-(3-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001005]** A solution of **Intermediate 846** (0.12 g, 0.12 mmol) in DCM (3.4 mL) and TFA (0.18 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.20 g). LCMS (Method 15): 2.58 min, 645.3 $[M+H]^+$.

**Intermediate 848:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001006]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 847** (77 mg, 0.12 mmol), azetidine (10 µL, 0.14 mmol), triethylamine (0.05 mL, 0.36 mmol) in DCM (1.3 mL) at RT for 1 h, then STAB (51 mg, 0.24 mmol) at RT for 1 h. Purified by catch and release chromatography (10 g SCX2, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (87 mg). LCMS (Method 15): 2.80 min, 686.3 $[M+H]^+$.

**Intermediate 849:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(azetidin-1-yl)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001007]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 848** (87 mg, 0.08 mmol) and 10% palladium on carbon (20 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 6 h, to provide the title compound (30 mg). LCMS (Method 15): 2.85 min, 688.4 $[M+H]^+$.

**Intermediate 850:** Ethyl (*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enamido)-3-(4,4'-difluoro-2',5-dimethyl-6'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[001008]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 237** (1.0 g, 2.20 mmol), *N*-Boc-*L*-allylglycine (0.52 g, 2.42 mmol, CAS 90600-20-7), DIPEA (1.15 mL, 6.61 mmol), HOBt (0.30 g, 2.20 mmol) and EDCI (0.51 g, 2.64 mmol) in MeCN (15 mL) at RT for 20 h. Purified by flash chromatography (24 g, silica gel, 0-40% EtOAc in petroleum ether) to provide the title compound (1.37 g). LCMS (Method 15): 2.67 min, 615.3 $[M+H]^+$.

**Intermediate 851:** Ethyl 2-((10*S*,13*S*)-10-((*tert*-butoxycarbonyl)amino)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[001009]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 850** (1.35 g, 2.09 mmol) in DCE (0.25 L) and Grubbs II (0.18 g, 0.21 mmol) at 50 °C for 1.5 h. Purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (1.05 g). LCMS (Method 11): 2.44 min, 609.5 $[M+Na]^+$.

**Intermediate 852:** Ethyl 2-((10*S*,13*S*)-10-((*tert*-butoxycarbonyl)amino)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[001010]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 851** (1.0 g, 1.62 mmol) and 10% palladium on carbon (0.10 g) in ethanol (15 mL) under a hydrogen atmosphere at RT for 6.5 h. Purified by flash chromatography (24 g silica gel, eluting 0-50%

EtOAc in petroleum ether) to provide the title compound (0.95 g). LCMS (Method 15): 2.57 min, 589.3 $[M+H]^+$.

**Intermediate 853:** Ethyl 2-((10*S*,13*S*)-10-amino-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate hydrochloride

**[001011]** A suspension of **Intermediate 852** (0.95 g, 1.57 mmol) in 4 M HCl in 1,4-dioxane (3.9 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (0.83 g). LCMS (Method 15): 2.23 min, 489.2 $[M+H]^+$.

**Intermediate 854:** 2-Iodo-3,5,6-trimethylphenol

**[001012]** Prepared in an analogous manner to **Intermediate 759** using 2,3,5-trimethylphenol (1.0 g, 6.68 mmol, CAS 697-82-5), sodium hydride (60% dispersion in oil, 0.55 g, 13.7 mol) in toluene (33 mL) at 0 °C for 30 min then iodine (1.69 g, 6.64 mmol) added portion wise over 2 h at RT. Purified by flash chromatography (40 g silica gel, eluting 0-10% EtOAc in petroleum ether) to provide the title compound (0.83 g). LCMS (Method 11): 2.11 min, 261.3 $[M-H]^-$.

**Intermediate 855**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-2'-hydroxy-3',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[001013]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 854** (0.66 g, 2.25 mmol), **Intermediate 377** (0.90 g, 1.89 mmol), $K_3PO_4$ (1.22 g, 5.72 mmol), palladium acetate (42 mg, 0.19 mmol) and tricyclohexyl phosphine (54 mg, 0.19 mmol) in toluene (10 mL) and water (2.5 mL) at 100 °C for 3 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (1.02 g). LCMS (Method 15): 2.62 min, 484.3 $[M-H]^-$.

**Intermediate 856:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-3',4',6'-trimethyl-2'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[001014]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 855** (1.02 g, 2.10 mmol), $K_2CO_3$ (0.44 g, 3.15 mmol) and 5-bromopent-1-ene (0.38 g, 2.52 mmol) in MeCN (26 mL) at 85 °C for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.76 g). LCMS (Method 15): 2.95 min, 552.3 $[M-H]^-$.

**Intermediate 857:** Ethyl (*S*)-3-amino-3-(5-cyclopropyl-4-fluoro-3',4',6'-trimethyl-2'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001015]** A suspension of **Intermediate 856** (0.76 g, 1.37 mmol) in 4 M HCl in 1,4-dioxane (3.4 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure to provide the title compound (0.67 g). LCMS (Method 15): 2.75 min, 454.2 $[M+H]^+$.

**Intermediate 858:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-3',4',6'-trimethyl-2'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[001016]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 857** (0.67 g, 1.37 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.25 g, 2.05 mmol, CAS 413622-10-3), DIPEA (0.73 mL, 4.10 mmol), HOBt (0.19 g, 1.37 mmol) and EDCI (0.31 g, 1.64 mmol) in MeCN (8 mL) at RT for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.49 g). LCMS (Method 15): 2.71 min, 552.3 $[M+H]^+$.

**Intermediate 859:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-3',4',6'-trimethyl-2'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[001017]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 858** (0.49 g, 0.89 mmol), triethylamine (0.28 mL, 1.78 mmol) and methanesulfonyl chloride (82 µL, 1.07 mmol) in DCM (6 mL) at RT for 5 h, to provide the title compound (0.56 g). LCMS (Method 15): 2.76 min, 630.3 $[M+H]^+$.

**Intermediate 860:** Ethyl (*S*)-3-(5-cyclopropyl-4-fluoro-3',4',6'-trimethyl-2'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[001018]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 859** (0.55 g, 0.87 mmol), **Intermediate 258** (0.25 g, 1.05 mmol) and $K_2CO_3$ (0.36 g, 3.0 mmol) in MeCN (9 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-6% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.19 g). LCMS (Method 15): 2.88 min, 768.3 $[M+H]^+$.

**Intermediate 861:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^3$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[001019]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 860** (0.19 g, 0.22 mmol) in DCE (0.13 L) and Grubbs II (24 mg, 28 µmol) at 50 °C for 3 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.16 g). LCMS (Method 15): 2.74 min, 740.4 $[M+H]^+$.

**Intermediate 862:** Ethyl 2-((10*S*,13*S*)-1$^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^3$,2$^4$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[001020]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 861** (0.16 g, 0.15 mmol) and 10% palladium on carbon (16 mg) in ethanol (7.5 mL) under a hydrogen atmosphere at RT for 4 h, to provide the title compound (0.16 g). LCMS (Method 15): 2.81 min, 742.3 $[M+H]^+$.

**Intermediate 863:** (*R*,*Z*)-*N*-(3-Bromo-5-(trifluoromethyl)benzylidene)-2-methylpropane-2-sulfinamide

**[001021]** Prepared in an analogous manner to **Intermediate 102** using 3-bromo-5-(trifluoromethyl)benzaldehyde (10.0 g, 43.6 mmol, CAS 477535-41-4), (*R*)-2-methylpropane-2-sulfinimide (5.28 g, 43.6 mmol, CAS 196929-78-9) and titanium ethoxide (13.6 g, 59.5 mmol) in THF (72 mL) at 40 °C for 18 h, to provide the title compound (12.1 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 8.57 (s, 1H), 8.16 (s, 1H), 8.01 (s, 1H), 7.89 (s, 1H), 1.28 (s, 9H).

**Intermediate 864:** Ethyl (*S*)-3-(3-bromo-5-(trifluoromethyl)phenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

**[001022]** Prepared in an analogous manner to **Intermediate 104** using zinc (6.98 g, 0.11 mol), chlorotrimethylsilane (0.54 mL, 4.27 mmol) and ethyl bromoacetate (5.92 mL, 53.5 mmol) in THF (0.10 L) at 65 °C for 1 h, then **Intermediate 863** (7.60 g, 21.3 mmol) in THF (22 mL) at RT for 1 h. Purified by dry flash chromatography (1 kg silica gel, eluting 0-30% EtOAc in petroleum ether) then flash chromatography (120 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (6.3 g). LCMS (Method 15): 2.22 min, 446.0 $[M+H]^+$.

**Intermediate 865:** Ethyl (*S*)-3-amino-3-(3-bromo-5-(trifluoromethyl)phenyl)propanoate

**[001023]** A solution of **Intermediate 864** (9.6 g, 21.6 mmol) in DCM (12.5 mL) and 4 M HCl in 1,4-dioxane (32 mL) was stirred at RT for 2 h. The mixture concentrated under reduced pressure, diluted with water and washed with EtOAc. The aqueous was basified with aqueous $NaHCO_3$ and extracted with EtOAc. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure, to provide the title compound (2.0 g). LCMS (Method 15): 1.99 min, 342.0 $[M+H]^+$.

**Intermediate 866:** Ethyl (*S*)-3-(3-bromo-5-(trifluoromethyl)phenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[001024]** To a stirred suspension of **Intermediate 865** (2.1 g, 6.17 mmol) and Boc anhydride (1.62 g, 7.41 mmol) in DCM (15 mL) was added DIPEA (1.61 mL, 9.26 mmol) and the mixture stirred at RT for 2 h. The reaction mixture was diluted with DCM and washed with 1 M aqueous HCl, water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (40 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (2.40 g). LCMS (Method 4): 2.36 min, 341.9 $[M\text{-}Boc+H]^+$.

**Intermediate 867**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-fluoro-2'-hydroxy-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001025]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 866** (0.10 g, 0.22 mmol), **Intermediate 821** (65 mg, 0.26 mmol), $K_3PO_4$ (0.14 g, 0.65 mmol), XPhosPdG2 (17 mg, 22 µmol) in 1,4-dioxane (4.1 mL) and water (1 mL) at 110 °C for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (35 mg). LCMS (Method 15): 2.37 min, 484.2 $[M\text{-}H]^-$.

**Intermediate 868:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-fluoro-2'-methyl-5-(trifluoromethyl)-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[001026]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 867** (0.83 g, 1.64 mmol), phenyl triflimide (0.58 g, 1.63 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (0.64 g, 1.95 mmol) in DCM (8.2 mL) at RT for 20 h. Purified by flash chromatography (25 g silica gel, eluting 0–30% EtOAc in petroleum ether) to provide the title compound (0.88 g). LCMS (Method 15): 2.65 min, 518.1 $[M\text{-}Boc+H]^+$.

**Intermediate 869:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001027]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 868** (0.59 g, 0.91 mmol), 5-hexenylboronic acid (0.26 g, 2.29 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.32 g, 2.29 mmol), RuPhosPdG3 (76 mg, 91 µmol) and RuPhos (43 mg, 91 µmol) in toluene (41 mL) and water (5 mL) at 95 °C for 1 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.45 g). LCMS (Method 15): 2.77 min, 452.4 $[M\text{-}Boc+H]^+$.

**Intermediate 870:** Ethyl (*S*)-3-amino-3-(4'-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001028]** A suspension of **Intermediate 869** (0.83 g, 1.29 mmol) in 4 M HCl in 1,4-dioxane (3.2 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure and purified by catch and release chromatography (10 g SCX, eluting MeOH followed

by 3.5 M ammonia in MeOH) to provide the title compound (0.58 g). LCMS (Method 15): 2.69 min, 452.1 $[M+H]^+$.

**Intermediate 871:** Ethyl (*S*)-3-(4'-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[001029]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 870** (0.58 g, 1.17 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.23 g, 1.75 mmol, CAS 413622-10-3), DIPEA (0.62 mL, 3.50 mmol), HOBt (0.20 g, 1.17 mmol) and EDCI (0.27 g, 1.40 mmol) in MeCN (11 mL) at RT for 72 h. Purified by flash chromatography (24 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.52 g). LCMS (Method 15): 2.65 min, 550.2 $[M+H]^+$.

**Intermediate 872:** Ethyl (*S*)-3-(4'-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[001030]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 871** (0.52 g, 0.95 mmol), triethylamine (0.26 mL, 1.90 mmol) and methanesulfonyl chloride (0.11 mL, 1.42 mmol) in DCM (6 mL) at RT for 1 h, to provide the title compound (0.70 g). LCMS (Method 15): 2.71 min, 628.3 $[M+H]^+$.

**Intermediate 873:** Ethyl (*S*)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4'-fluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001031]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 872** (0.57 g, 0.90 mmol), **Intermediate 258** (0.23 g, 0.99 mmol) and $K_2CO_3$ (0.37 g, 2.7 mmol) in MeCN (9 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-8% MeOH in DCM) to provide the title compound (0.23 g). LCMS (Method 15): 2.87 min, 766.4 $[M+H]^+$.

**Intermediate 874:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001032]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 873** (0.23 g, 0.30 mmol) in DCE (0.20 L) and Grubbs II (26 mg, 30 µmol) at 50 °C for 2 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.21 g). LCMS (Method 15): 2.72 min, 738.3 $[M+H]^+$.

**Intermediate 875:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001033]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 874** (0.21 g, 0.23 mmol) and 10% palladium on carbon (24 mg) in ethanol (4.4 mL) under a hydrogen atmosphere at RT for 4 h. Purified by flash chromatography (12 g silica gel, eluting 5-10% MeOH in DCM) to provide the title compound (0.12 g). LCMS (Method 15): 2.74 min, 740.3 $[M+H]^+$.

**Intermediate 876:** (*R*,*Z*)-*N*-(5-Bromo-2-fluoro-4-methylbenzylidene)-2-methylpropane-2-sulfinamide

**[001034]** Prepared in an analogous manner to **Intermediate 102** using 5-bromo-2-fluoro-4-methylbenzaldehyde (10.0 g, 46.1 mmol, CAS 497224-12-1), (*R*)-2-methylpropane-2-sulfinimide (6.14 g, 50.7 mmol, CAS 196929-78-9) and titanium ethoxide (15.8 g, 69.1 mmol) in THF (96 mL) at 40 °C for 3 h, to provide the title compound (12.3 g). LCMS (Method 15): 2.32 min, 319.9 $[M+H]^+$.

**Intermediate 877:** Ethyl (*S*)-3-(5-bromo-2-fluoro-4-methylphenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

**[001035]** Prepared in an analogous manner to **Intermediate 104** using zinc (7.45 g, 0.11 mol), chlorotrimethylsilane (0.58 mL, 4.56 mmol) and ethyl bromoacetate (6.32 mL, 57.0 mmol) in THF (0.12 L) at 60 °C for 1 h, then **Intermediate 876** (7.30 g, 22.8 mmol) in THF (25 mL) at RT for 30 min. Purified by flash chromatography (80 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (8.15 g). LCMS (Method 15): 2.09 min, 410.0 $[M+H]^+$.

**Intermediate 878:** Ethyl (*S*)-3-amino-3-(5-bromo-2-fluoro-4-methylphenyl)propanoate

**[001036]** A solution of **Intermediate 877** (9.6 g, 21.6 mmol) in ethanol (12.6 mL) and 4 M HCl in 1,4-dioxane (39 mL) was stirred at RT for 2 h. The mixture concentrated under reduced pressure, diluted with water and washed with EtOAc. The aqueous was basified with aqueous $NaHCO_3$ and extracted with EtOAc. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure, to provide the title compound (8.03 g). LCMS (Method 15): 1.82 min, 306.0 $[M+H]^+$.

**Intermediate 879:** Ethyl (*S*)-3-(5-bromo-2-fluoro-4-methylphenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[001037]** To a stirred suspension of **Intermediate 878** (8.0 g, 22.6 mmol) and Boc anhydride (5.92 g, 27.1 mmol) in DCM (54 mL) was added DIPEA (5.91 mL, 33.9 mmol) and the mixture stirred at RT for 64 h. The reaction mixture was diluted with DCM and washed with 1 M aqueous HCl, water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (40 g silica gel, eluting 0-

40% EtOAc in petroleum ether) to provide the title compound (8.02 g). LCMS (Method 15): 2.29 min, 306.0 $[M\text{-}Boc+H]^+$.

**Intermediate 880:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate

**[001038]** Prepared in an analogous manner to **Intermediate 2** using **Intermediate 879** (2.50 g, 6.00 mmol), bis(pinacolato)diboron (1.83 g, 7.20 mmol), potassium acetate (1.47 g, 15.0 mmol), $Pd(dppf)Cl_2$ (0.44 g, 0.60 mmol) in 1,4-dioxane (23 mL) at 90 °C for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (1.76 g). LCMS (Method 15): 2.55 min, 352.2 $[M\text{-}Boc+H]^+$.

**Intermediate 881**: Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-chloro-4,4',6'-trifluoro-6-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001039]** Prepared in an analogous manner to **Intermediate 3** using 2-bromo-1-chloro-3,5-difluorobenzene (0.76 g, 3.35 mmol, CAS 1020198-58-6), **Intermediate 880** (1.20 g, 2.23 mmol), $K_3PO_4$ (1.42 g, 6.70 mmol), potassium formate (0.19 g, 2.23 mmol) and $Pd(dtbpf)Cl_2$ (72 mg, 0.11 mmol) in toluene (31 mL) and water (7 mL) at 90 °C for 3 h. Purified by flash chromatography (25 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.79 g). LCMS (Method 21): 5.19 min, 372.1 $[M\text{-}Boc+H]^+$.

**Intermediate 882:** Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-6-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001040]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 881** (0.37 g, 0.79 mmol), 5-hexenylboronic acid (0.15 g, 1.19 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.33 g, 2.37 mmol), palladium acetate (36 mg, 0.16 mmol) and SPhos (0.13 g, 0.32 mmol) in toluene (6 mL) and water (2 mL) at 90 °C for 2 h. Additional 5-hexenylboronic acid (51 mg, 0.40 mmol), palladium acetate (18 mg, 0.08 mmol) and SPhos (65 mg, 0.16 mmol) added and heated at 90 °C for 1 h. Purified by flash chromatography (25 g silica gel, eluting 0-25% EtOAc in petroleum ether) to provide the title compound (0.65 g). LCMS (Method 15): 2.80 min, 420.2 $[M\text{-}Boc+H]^+$.

**Intermediate 883:** Ethyl (3*S*)-3-amino-3-(2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-6-methyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001041]** A suspension of **Intermediate 882** (0.65 g, 1.24 mmol) in 4 M HCl in 1,4-dioxane (3.1 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.69 g). LCMS (Method 15): 2.59 min, 420.2 $[M+H]^+$.

**Intermediate 884:** Ethyl (3*S*)-3-((*R*)-2-hydroxypent-4-enamido)-3-(2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-6-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001042]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 883** (0.69 g, 1.24 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.24 g, 1.90 mmol, CAS 413622-10-3), DIPEA (0.66 mL, 3.72 mmol), HOBt (0.17 g, 1.24 mmol) and EDCI (0.28 g, 1.49 mmol) in MeCN (7 mL) at RT for 16 h. Purified by flash chromatography (25 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.37 g). LCMS (Method 15): 2.51 min, 518.2 $[M+H]^+$.

**Intermediate 885:** Ethyl (3*S*)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)-3-(2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-6-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001043]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 884** (0.37 g, 0.67 mmol), triethylamine (0.19 mL, 1.34 mmol) and methanesulfonyl chloride (78 µL, 1.01 mmol) in DCM (4 mL) at RT for 1 h, to provide the title compound (0.38 g). LCMS (Method 15): 2.60 min, 596.3 $[M+H]^+$.

**Intermediate 886:** Ethyl (3*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-6-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001044]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 885** (0.38 g, 0.55 mmol), **Intermediate 258** (0.14 g, 0.60 mmol) and $K_2CO_3$ (0.23 g, 1.64 mmol) in MeCN (5 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-10% (5% ammonia MeOH) in DCM) to provide the title compound (0.23 g). LCMS (Method 15): 2.76 min, 734.3 $[M+H]^+$.

**Intermediate 887:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$-trifluoro-$2^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001045]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 886** (0.23 g, 0.29 mmol) in DCE (0.14 L) and Grubbs II (24 mg, 28 µmol) at 50 °C for 4 h. Conditions repeated at 50 °C for 2h. Purified by flash chromatography (25 g silica gel, eluting 0-10% (5% ammonia MeOH) in DCM) to provide the title compound (0.14 g). LCMS (Method 15): 2.63 min, 706.3 $[M+H]^+$.

**Intermediate 888:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$-trifluoro-$2^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001046]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 887** (0.14 g, 0.18 mmol) and 10% palladium on carbon (19 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 5.5 h. Purified by flash chromatography (12 g silica gel, eluting

0-10% MeOH in DCM) to provide the title compound (0.12 g). LCMS (Method 15): 2.67 min, 708.3 $[M+H]^+$.

**Intermediate 889:** (*R*,*Z*)-*N*-(3-Bromo-5-methylbenzylidene)-2-methylpropane-2-sulfinamide

**[001047]** Prepared in an analogous manner to **Intermediate 102** using 3-bromo-5-methylbenzaldehyde (10.6 g, 53.2 mmol, CAS 188813-04-9), (*R*)-2-methylpropane-2-sulfinimide (7.09 g, 58.5 mmol, CAS 196929-78-9) and titanium ethoxide (18.2 g, 79.7 mmol) in THF (86 mL) at 40 °C for 18 h, to provide the title compound (15.6 g). LCMS (Method 15): 2.26 min, 303.9 $[M+H]^+$.

**Intermediate 890:** Ethyl (*S*)-3-(3-bromo-5-methylphenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

**[001048]** Prepared in an analogous manner to **Intermediate 104** using zinc (5.41 g, 82.7 mmol), chlorotrimethylsilane (0.42 mL, 3.31 mmol) and ethyl bromoacetate (4.59 mL, 41.4 mmol) in THF (79 mL) at 60 °C for 1 h, then **Intermediate 889** (5.0 g, 16.5 mmol) in THF (17 mL) at RT for 3 h. Purified by flash chromatography (120 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (2.4 g). LCMS (Method 15): 2.12 min, 392.0 $[M+H]^+$.

**Intermediate 891:** Ethyl (*S*)-3-amino-3-(3-bromo-5-methylphenyl)propanoate

**[001049]** A solution of **Intermediate 890** (3.5 g, 8.52 mmol) in DCM (4.9 mL) and 4 M HCl in 1,4-dioxane (12.7 mL) was stirred at RT for 4 h. The mixture was basified with aqueous $NaHCO_3$ and extracted with EtOAc. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure, to provide the title compound (1.50 g). LCMS (Method 15): 1.82 min, 288.0 $[M+H]^+$.

**Intermediate 892:** Ethyl (*S*)-3-(3-bromo-5-methylphenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[001050]** To a stirred suspension of **Intermediate 891** (1.5 g, 5.24 mmol) and Boc anhydride (1.37 g, 6.29 mmol) in DCM (12 mL) was added DIPEA (1.37 mL, 7.86 mmol) and the mixture stirred at RT for 2 h. The reaction mixture was diluted with DCM and washed with 1 M aqueous HCl, water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (8.02 g). LCMS (Method 11): 2.24 min, 286.1 $[M-Boc+H]^+$.

**Intermediate 893**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-fluoro-2'-hydroxy-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[001051]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 892** (0.10 g, 0.25 mmol), **Intermediate 821** (93 mg, 0.37 mmol), $K_3PO_4$ (0.16 g, 0.74 mmol), XPhosPdG2 (19 mg, 25 µmol) in 1,4-dioxane (4.1 mL) and water (1 mL) at 110 °C for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (45 mg). LCMS (Method 15): 2.25 min, 430.2 $[M-H]^-$.

**Intermediate 894:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-fluoro-2',5-dimethyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[001052]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 893** (45 mg, 0.09 mmol), phenyl triflimide (32 mg, 0.09 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (35 mg, 0.11 mmol) in DCM (0.5 mL) at RT for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0–20% EtOAc in petroleum ether) to provide the title compound (33 mg). LCMS (Method 11): 2.54 min, 562.5 $[M-H]^-$.

**Intermediate 895:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-fluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[001053]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 894** (0.68 g, 1.15 mmol), 5-hexenylboronic acid (0.20 g, 1.72 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.48 g, 3.44 mmol), palladium acetate (26 mg, 0.12 mmol) and RuPhos (80 mg, 0.17 mmol) in toluene (11 mL) and water (1.2 mL) at 100 °C for 1.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.54 g). LCMS (Method 15): 2.88 min, 496.3 $[M-H]^-$.

**Intermediate 896:** Ethyl (*S*)-3-amino-3-(4'-fluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001054]** A suspension of **Intermediate 895** (0.74 g, 1.39 mmol) in 4 M HCl in 1,4-dioxane (3.5 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.81 g). LCMS (Method 15): 2.66 min, 398.2 $[M+H]^+$.

**Intermediate 897:** Ethyl (*S*)-3-(4'-fluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[001055]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 896** (0.81 g, 1.39 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.26 g, 2.08 mmol, CAS 413622-10-3), DIPEA (0.74 mL, 4.16 mmol), HOBt (0.23 g, 1.39 mmol) and EDCI (0.32 g, 1.67 mmol) in MeCN (13 mL) at RT for 16 h. Purified by flash chromatography (24 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.51 g). LCMS (Method 15): 2.61 min, 496.2 $[M+H]^+$.

**Intermediate 898:** Ethyl (*S*)-3-(4'-fluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[001056]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 897** (0.51 g, 0.90 mmol), triethylamine (0.25 mL, 1.79 mmol) and methanesulfonyl chloride (0.10 mL, 1.35 mmol) in DCM (8 mL) at RT for 1 h, to provide the title compound (0.70 g). LCMS (Method 15): 2.68 min, 574.3 $[M+H]^+$.

**Intermediate 899:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4'-fluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[001057]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 898** (0.70 g, 0.91 mmol), **Intermediate 258** (0.23 g, 1.00 mmol) and $K_2CO_3$ (0.38 g, 2.73 mmol) in MeCN (11 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica gel, eluting 10-90% EtOAc in petroleum ether) to provide the title compound (0.20 g). LCMS (Method 15): 2.85 min, 712.3 $[M+H]^+$.

**Intermediate 900:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001058]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 899** (0.20 g, 0.25 mmol) in DCE (0.12 L) and Grubbs II (21 mg, 25 µmol) at 50 °C for 2 h. Conditions repeated at 50 °C for 2h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.16 g). LCMS (Method 15): 2.70 min, 684.3 $[M+H]^+$.

**Intermediate 901:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001059]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 900** (0.16 g, 0.19 mmol) and 10% palladium on carbon (20 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 4 h. Purified by flash chromatography (12 g silica gel, eluting 5-10% MeOH in DCM) to provide the title compound (0.14 g). LCMS (Method 15): 2.74 min, 686.3 $[M+H]^+$.

**Intermediate 902:** (*R*,*E*)-*N*-(3-Bromo-2-fluoro-5-(trifluoromethyl)benzylidene)-2-methylpropane-2-sulfinamide

**[001060]** Prepared in an analogous manner to **Intermediate 102** using 3-bromo-2-fluoro-5-(trifluoromethyl)benzaldehyde (10.2 g, 37.6 mmol, CAS 1236538-66-1), (*R*)-2-

methylpropane-2-sulfinimide (5.01 g, 41.4 mmol, CAS 196929-78-9) and titanium ethoxide (12.9 g, 56.4 mmol) in THF (61 mL) at 40 °C for 18 h, to provide the title compound (13.6 g). LCMS (Method 15): 2.35 min, 375.9 $[M+H]^+$.

**Intermediate 903:** Ethyl (*S*)-3-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

**[001061]** Prepared in an analogous manner to **Intermediate 104** using zinc (8.66 g, 0.13 mol), chlorotrimethylsilane (0.67 mL, 5.30 mmol) and ethyl bromoacetate (7.34 mL, 66.2 mmol) in THF (79 mL) at 60 °C for 2 h, then **Intermediate 902** (10.0 g, 25.6 mmol) in THF (24 mL) at RT for 40 min. Purified by dry flash chromatography (silica gel, eluting 0-25% EtOAc in petroleum ether) to provide the title compound (3.92 g). LCMS (Method 15): 2.19 min, 462.0 $[M+H]^+$.

**Intermediate 904:** Ethyl (*S*)-3-amino-3-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)propanoate

**[001062]** A solution of **Intermediate 903** (3.92 g, 8.44 mmol) in 4 M HCl in 1,4-dioxane (42 mL) was stirred at RT for 2.5 h. The mixture was concentrated under reduced pressure, basified with aqueous $NaHCO_3$ and extracted with EtOAc. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure, to provide the title compound (3.0 g). LCMS (Method 15): 1.97 min, 357.9 $[M+H]^+$.

**Intermediate 905:** Ethyl (*S*)-3-(3-bromo-2-fluoro-5-(trifluoromethyl)phenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[001063]** To a stirred suspension of **Intermediate 904** (2.96 g, 8.27 mmol) and Boc anhydride (1.98 g, 9.09 mmol) in DCM (55 mL) was added triethyamine (1.73 mL, 12.4 mmol) and the mixture stirred at RT for 24 h. The reaction mixture was washed with water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (1.46 g). LCMS (Method 15): 2.41 min, 357.9 $[M-Boc+H]^+$.

**Intermediate 906**: Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2,4'-difluoro-2'-hydroxy-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001064]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 905** (0.86 g, 1.65 mmol), **Intermediate 821** (0.34 g, 1.24 mmol), $K_3PO_4$ (1.05 g, 4.96 mmol), XPhosPdG2 (0.13 g, 0.17 mmol) in 1,4-dioxane (26 mL) and water (6.6 mL) at 110 °C for 1 h. Purified by flash chromatography (40 g silica gel, eluting 0-15% EtOAc in petroleum ether) to provide the title compound (0.30 g). LCMS (Method 15): 2.31 min, 404.1 $[M-Boc+H]^+$.

**Intermediate 907:** Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2,4'-difluoro-2'-methyl-5-(trifluoromethyl)-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[001065]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 906** (0.67 g, 1.20 mmol), phenyl triflimide (0.43 g, 1.44 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (0.49 g, 1.44 mmol) in DCM (6 mL) at RT for 2 h. Purified by flash chromatography (40 g silica gel, eluting 0–40% EtOAc in petroleum ether) to provide the title compound (0.59 g). LCMS (Method 15): 2.64 min, 634.2 $[M-H]^-$.

**Intermediate 908:** Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001066]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 907** (0.54 g, 0.85 mmol), 5-hexenylboronic acid (0.15 g, 1.18 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.35 g, 2.56 mmol), palladium acetate (19 mg, 0.09 mmol) and RuPhos (59 mg, 0.13 mmol) in toluene (5 mL) and water (1.5 mL) at 95 °C for 1 h. Purified by flash chromatography (25 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.42 g). $^1H$ NMR (400 MHz; $CDCl_3$) δ: 7.63 (dd, 1H), 7.34 (dd, 1H), 6.92 – 6.79 (m, 2H), 5.88 – 5.60 (m, 2H), 5.44 – 5.32 (m, 1H), 4.98 – 4.85 (m, 2H), 4.11 – 4.01 (m, 2H), 2.95 – 2.76 (m, 2H), 2.39 – 2.15 (m, 2H), 2.03 – 1.86 (m, 5H), 1.49 – 1.33 (m, 11H), 1.28 – 1.20 (m, 2H), 1.14 (td, 3H).

**Intermediate 909:** Ethyl (3*S*)-3-amino-3-(2,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001067]** A suspension of **Intermediate 908** (0.42 g, 0.69 mmol) in 4 M HCl in 1,4-dioxane (1.7 mL) was stirred at RT for 2.5 h. The mixture was concentrated under reduced pressure to provide the title compound (0.47 g). LCMS (Method 15): 2.66 min, 470.2 $[M+H]^+$.

**Intermediate 910:** Ethyl (3*S*)-3-(2,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[001068]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 909** (0.47 g, 0.66 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.13 g, 0.99 mmol, CAS 413622-10-3), DIPEA (0.35 mL, 2.03 mmol), HOBt (89 mg, 0.66 mmol) and EDCI (0.15 g, 0.79 mmol) in MeCN (6.6 mL) at RT for 19 h. Purified by flash chromatography (12 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.33 g). LCMS (Method 15): 2.63 min, 568.2 $[M+H]^+$.

**Intermediate 911:** Ethyl (3*S*)-3-(2,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[001069]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 910** (0.33 g, 0.56 mmol), triethylamine (0.16 mL, 1.11 mmol) and methanesulfonyl chloride (65 µL, 0.84 mmol) in DCM (7 mL) at RT for 2 h, to provide the title compound (0.42 g). LCMS (Method 15): 2.68 min, 644.3 $[M-H]^-$.

**Intermediate 912:** Ethyl (3*S*)-3-(2,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[001070]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 911** (0.36 g, 0.55 mmol), **Intermediate 258** (0.14 g, 0.61 mmol) and $K_2CO_3$ (0.27 g, 1.94 mmol) in MeCN (7 mL) at reflux for 2 h. Purified by reverse phase chromatography (C18, eluting 40-50% MeCN in 0.1% aqueous formic acid) to provide the title compound (0.19 g). LCMS (Method 15): 2.84 min, 784.3 $[M+H]^+$.

**Intermediate 913:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^2$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001071]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 912** (0.19 g, 0.22 mmol) in DCE (0.11 L) and Grubbs II (20 mg, 23 µmol) at 50 °C for 4.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.16 g). LCMS (Method 15): 2.70 min, 756.3 $[M+H]^+$.

**Intermediate 914:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^2$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001072]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 913** (0.16 g, 0.20 mmol) and 10% palladium on carbon (22 mg) in ethanol (2 mL) under a hydrogen atmosphere at RT for 4 h. Purified by flash chromatography (12 g silica gel, eluting 0-3% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.12 g). LCMS (Method 15): 2.76 min, 758.4 $[M+H]^+$.

**Intermediate 915:** 2,3-Difluoro-6-iodo-5-methylphenol

**[001073]** Prepared in an analogous manner to **Intermediate 759** using 2,3-difluoro-5-methylphenol (5.8 g, 34.2 mmol, CAS 886037-58-7), sodium hydride (60% dispersion in oil, 2.8 g, 70.0 mmol) in toluene (50 mL) at 0 °C for 30 min then iodine (8.6 g, 33.9 mmol) added portion wise over 30 min at RT. Purified by flash chromatography (80 g silica gel, eluting 0-10% EtOAc in petroleum ether) to provide the title compound (6.8 g). LCMS (Method 15): 1.88 min, 268.9 $[M-H]^-$.

**Intermediate 916**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-3',4,4'-trifluoro-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001074]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 915** (0.99 g, 2.93 mmol), **Intermediate 377** (1.50 g, 2.92 mmol), $K_3PO_4$ (1.24 g, 5.84 mmol), palladium acetate (66 mg, 0.29 mmol) and SPhos (0.12 g, 0.29 mmol) in toluene (40 mL) and water (4 mL) at 85 °C for 24 h. Purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.45 g). LCMS (Method 7): 2.46 min, 492.6 $[M-H]^-$.

**Intermediate 917:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-3',4,4'-trifluoro-6'-methyl-2'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[001075]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 916** (1.47 g, 2.74 mmol), $K_2CO_3$ (0.60 g, 4.34 mmol) and 5-bromopent-1-ene (0.75 g, 5.07 mmol) in MeCN (10 mL) at 85 °C for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (1.29 g). LCMS (Method 7): 2.85 min, 462.2 $[M-Boc+H]^+$.

**Intermediate 918:** Ethyl (*S*)-3-amino-3-(5-cyclopropyl-3',4,4'-trifluoro-6'-methyl-2'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001076]** A suspension of **Intermediate 917** (1.29 g, 2.18 mmol) in 4 M HCl in 1,4-dioxane (6.0 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (1.20 g). LCMS (Method 7): 1.94 min, 462.2 $[M+H]^+$.

**Intermediate 919:** Ethyl (*S*)-3-(5-cyclopropyl-3',4,4'-trifluoro-6'-methyl-2'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[001077]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 918** (1.20 g, 2.22 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.29 g, 2.25 mmol, CAS 413622-10-3), DIPEA (1.20 mL, 6.89 mmol), HOBt (0.38 g, 2.22 mmol) and EDCI (0.56 g, 2.92 mmol) in MeCN (20 mL) at RT for 19 h. Extra (2*R*)-2-hydroxypent-4-enoic acid (0.29 g, 2.25 mmol) and HOBt (0.38 g, 2.22 mmol) were added and stirred at RT for 3 h. Purified by flash chromatography (25 g silica gel, eluting 0-5% MeOH in DCM) to provide the title compound (0.67 g). LCMS (Method 7): 2.59 min, 560.3 $[M+H]^+$.

**Intermediate 920:** Ethyl (*S*)-3-(5-cyclopropyl-3',4,4'-trifluoro-6'-methyl-2'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[001078]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 919** (0.65 g, 1.16 mmol), triethylamine (0.32 mL, 2.32 mmol) and methanesulfonyl chloride (0.14

mL, 1.74 mmol) in DCM (7 mL) at RT for 2 h, to provide the title compound (0.78 g). LCMS (Method 11): 2.63 min, 638.2 $[M+H]^+$.

**Intermediate 921:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-3',4,4'-trifluoro-6'-methyl-2'-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-yl)propanoate

**[001079]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 920** (0.74 g, 1.16 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.37 g, 1.51 mmol, CAS 109919-32-6) and $K_2CO_3$ (0.48 g, 3.48 mmol) in MeCN (11 mL) at reflux for 18 h. Purified by flash chromatography (24 g silica gel, 0-25% EtOAc in petroleum ether) to provide the title compound (0.32 g). LCMS (Method 15): 2.84 min, 783.2 $[M+H]^+$.

**Intermediate 922:** Ethyl 2-((10*S*,13*S*)-10-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$-cyclopropyl-$1^4$,$2^3$,$2^4$-trifluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[001080]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 921** (0.30 g, 0.38 mmol) in DCE (0.13 L) and Grubbs II (32 mg, 38 µmol) at 50 °C for 1.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.25 g). LCMS (Method 11): 2.72 min, 757.1 $[M+H]^+$.

**Intermediate 923:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^3$,$2^4$-trifluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[001081]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 922** (0.25 g, 0.31 mmol), $Pd(PPh_3)_2Cl_2$ (15 mg, 22 µmol), copper(I) iodide (4.2 mg, 22 µmol), triethylamine (0.31 mL, 2.19 mmol) and *N*,*N*-dimethylpropargylamine (0.24 mL, 2.19 mmol, CAS 7223-38-3) in MeCN (7 mL) at 80 °C for 24 h. Conditions repeated. Purified by flash chromatography (12 g silica gel, eluting 0-5% (0.5% ammonia MeOH) in DCM) then catch and release chromatography (2 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.12 g). LCMS (Method 15): 2.64 min, 758.3 $[M+H]^+$.

**Intermediate 924:** Ethyl 2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^3$,$2^4$-trifluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[001082]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 923** (0.12 g, 0.16 mmol) and 10% palladium on carbon (17 mg) in ethanol (4 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-5% (0.1% ammonia MeOH) in DCM) to provide the title compound (61 mg). LCMS (Method 15): 2.77 min, 764.4 $[M+H]^+$.

**Intermediate 925:** (*S*)-2-Hydroxy-4-methylpent-4-enoic acid

**[001083]** To a solution of (2*R*)-2-amino-4-methyl-pent-4-enoic acid (1.22 g, 9.45 mmol, CAS 905929-81-9) in AcOH (15 mL) and water (39 mL) at 0 °C was added a solution of sodium nitrite (1.30 g, 18.9 mmol) in water (2 mL) was added dropwise, then the mixture was stirred at 0 °C for 1.5 h. The mixture was quenched with methylamine (2 M in THF, 9.65 mL) at 0 °C for 30 min. The reaction was diluted with 2 M aqueous HCl and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (80 g, silica, 0–10% MeOH in (1% AcOH in DCM)) to provide the title compound (0.33 g). $^1$H NMR (500 MHz; $CDCl_3$) δ: 4.96 (d, 1H), 4.87 (s, 1H), 4.41 – 4.38 (m, 1H), 2.66 – 2.61 (m, 1H), 2.42 (dd, 1H), 1.81 (s, 3H) – OH signals not observed.

**Intermediate 926:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-hydroxy-4-methylpent-4-enamido)propanoate

**[001084]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 636** (1.28 g, 2.53 mmol), **Intermediate 925** (0.49 g, 3.79 mmol), DIPEA (1.76 mL, 10.1 mmol), HOBt (0.38 g, 2.78 mmol) and EDCI (0.73 g, 3.79 mmol) in MeCN (23 mL) at RT for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (1.14 g). LCMS (Method 22): 2.11 min, 582.3 $[M+H]^+$.

**Intermediate 927:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-4-methyl-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[001085]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 926** (0.79 g, 1.36 mmol), triethylamine (0.38 mL, 2.71 mmol) and methanesulfonyl chloride (0.16 mL, 2.04 mmol) in DCM (9 mL) at RT for 1 h, to provide the title compound (1.03 g). LCMS (Method 22): 2.13 min, 660.2 $[M+H]^+$.

**Intermediate 928:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpent-4-enamido)propanoate

**[001086]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 927** (0.90 g, 1.36 mmol), **Intermediate 258** (0.38 g, 1.63 mmol) and $K_2CO_3$ (0.56 g, 4.07 mmol) in MeCN (14 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-2% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.33 g). LCMS (Method 15): 2.91 min, 798.3 $[M+H]^+$.

**Intermediate 929:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,8-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001087]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 928** (0.27 g, 0.34 mmol) in DCE (0.11 L) and Grubbs II (29 mg, 34 µmol) at 50 °C for 4 h. Conditions repeated at 50 °C for 4 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.14 g). LCMS (Method 22): 2.82 min, 770.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.73 min, 756.3 $[M-14+H]^+$.

**Intermediate 930:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,8-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001088]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 929** (0.14 g, 0.18 mmol) and 10% palladium on carbon (19 mg) in ethanol (6 mL) under a hydrogen atmosphere at RT for 40 h. Purified by flash chromatography (4 g silica gel, eluting 0-10% (0.1% ammonia MeOH) in DCM) to provide the title compound (99 mg). LCMS (Method 15): 2.85 min, 772.4 $[M+H]^+$; 2.77 min olefin isomerisation metathesis product: 758.3 $[M-14+H]^+$.

**Intermediate 931**: Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4,4'-difluoro-2'-hydroxy-6,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[001089]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 879** (1.35 g, 3.34 mmol), **Intermediate 821** (1.82 g, 6.48 mmol), $K_3PO_4$ (2.06 g, 6.48 mmol), XPhosPdG2 (0.25 g, 0.32 mmol) in 1,4-dioxane (60 mL) at 90 °C for 4 h. Purified by flash chromatography (40 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (0.53 g). LCMS (Method 15): 2.31 min, 350.1 $[M-Boc+H]^+$.

**Intermediate 932:** Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4,4'-difluoro-2',6-dimethyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[001090]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 931** (0.95 g, 2.11 mmol), phenyl triflimide (0.90 g, 2.53 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (0.82 g, 2.53 mmol) in DCM (28 mL) at RT for 16 h. Purified by flash chromatography (25 g silica gel, eluting 0–50% EtOAc in petroleum ether) to provide the title compound (0.95 g). LCMS (Method 15): 2.62 min, 482.1 $[M-Boc+H]^+$.

**Intermediate 933:** Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[001091]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 932** (0.48 g, 0.82 mmol), 5-hexenylboronic acid (0.16 g, 1.23 mmol, CAS 1072952-16-9), $K_2CO_3$

(0.34 g, 2.46 mmol), palladium acetate (18 mg, 0.08 mmol) and RuPhos (57 mg, 0.12 mmol) in toluene (5 mL) and water (1.7 mL) at 100 °C for 2.5 h. Purified by flash chromatography (25 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.37 g). LCMS (Method 15): 2.87 min, 416.3 $[M-Boc+H]^+$.

**Intermediate 934:** Ethyl (3*S*)-3-amino-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001092]** A suspension of **Intermediate 933** (0.66 g, 1.29 mmol) in 4 M HCl in 1,4-dioxane (3.2 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.61 g). LCMS (Method 15): 2.65 min, 416.3 $[M+H]^+$.

**Intermediate 935:** Ethyl (3*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[001093]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 934** (0.61 g, 1.28 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.25 g, 1.95 mmol, CAS 413622-10-3), DIPEA (0.68 mL, 3.83 mmol), HOBt (0.17 g, 1.27 mmol) and EDCI (0.29 g, 1.53 mmol) in MeCN (7 mL) at RT for 23 h. Extra (2*R*)-2-hydroxypent-4-enoic acid (74 mg, 0.64 mmol) and EDCI (0.12 g, 0.64 mmol) were added and stirred at RT for 2 h. Purified by flash chromatography (25 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.45 g). LCMS (Method 15): 2.61 min, 514.2 $[M+H]^+$.

**Intermediate 936:** Ethyl (3*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[001094]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 935** (0.45 g, 0.82 mmol), triethylamine (0.34 mL, 2.47 mmol) and methanesulfonyl chloride (0.17 mL, 1.86 mmol) in DCM (5 mL) at RT for 4 h, to provide the title compound (0.65 g). LCMS (Method 15): 2.66 min, 592.2 $[M+H]^+$.

**Intermediate 937:** Ethyl (3*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[001095]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 936** (0.65 g, 0.76 mmol), **Intermediate 258** (0.20 g, 0.84 mmol) and $K_2CO_3$ (0.32 g, 2.28 mmol) in MeCN (6.5 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-10% (5% ammonia MeOH) in DCM) and again (25 g silica gel, eluting 0-5% (5% ammonia MeOH) in DCM) to provide the title compound (0.25 g). LCMS (Method 15): 2.82 min, 730.3 $[M+H]^+$.

**Intermediate 938:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001096]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 937** (0.25 g, 0.30 mmol) in DCE (0.14 L) and Grubbs II (26 mg, 30 µmol) at 50 °C for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.21 g). LCMS (Method 15): 2.70 min, 702.3 $[M+H]^+$.

**Intermediate 939:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001097]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 938** (0.21 g, 0.21 mmol) and 10% palladium on carbon (22 mg) in ethanol (11 mL) under a hydrogen atmosphere at RT for 4.5 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.17 g). LCMS (Method 15): 2.74 min, 704.3 $[M+H]^+$.

**Intermediate 940:** Ethyl 2-((10*S*,13*S*)-10-((3-((*tert*-butoxycarbonyl)(methyl)amino)propyl)amino)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[001098]** To a solution of **Intermediate 853** (0.15 g, 0.29 mmol) in EtOAc (4.5 mL) and IPA (1.5 mL) was added triethylamine (0.20 mL, 1.43 mmol) and *tert*-butyl *N*-methyl-*N*-(3-oxopropyl)carbamate (54 mg, 0.29 mmol, CAS 273757-11-2) in EtOAc (2.3 mL) and IPA (0.8 mL) at RT and stirred for 15 min. STAB (0.32 g, 1.48 mmol) was added and the mixture stirred at RT for 16 h. The mixture was diluted with water and extracted with EtOAc. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g silica gel, eluting 0-5% MeOH in DCM) to provide the title compound (0.12 g). LCMS (Method 15): 2.54 min, 660.4 $[M+H]^+$.

**Intermediate 941:** Ethyl 2-((10*S*,13*S*)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-10-(3-methyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[001099]** To a solution of **Intermediate 940** (0.12 g, 0.18 mmol) in DCM (14 mL) was added 4 M HCl in 1,4-dioxane (0.45 mL) and the mixture was stirred at RT for 3 h. The mixture was concentrated under reduced pressure. The residue was dissolved in MeCN (14 mL) then triethylamine (75 µL, 0.54 mmol) and CDI (58 mg, 0.36 mmol) were added and stirred at RT for 3 h. The mixture was concentrated under reduced pressure. The residue was dissolved in MeCN (30 mL) and AcOH (0.5 mL) and heated at 65 °C for 2 days. The mixture was

concentrated under reduced pressure and purified by flash chromatography (12 g silica gel, eluting 0-5% MeOH in DCM) to provide the title compound (0.10 g). LCMS (Method 15): 2.39 min, 586.3 $[M+H]^+$.

**Intermediate 942:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001100]** A solution of **Intermediate 747** (0.14 g, 0.12 mmol) in DCM (4.1 mL) and TFA (0.19 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure then dissolved in DCM (14 mL). 3-Methoxyazetidine hydrochloride (18 mg, 0.15 mmol, CAS 148644-09-1), triethylamine (69 µL, 0.50 mmol) and 4 Å molecular sieves were added and stirred at RT for 15 min. STAB (53 mg, 0.25 mmol) was added and stirred at RT for 3 h. The mixture was filtered and filtrate concentrated under reduced pressure and purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (69 mg). LCMS (Method 15): 2.67 min, 798.3 $[M+H]^+$.

**Intermediate 943:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001101]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 942** (68 mg, 85 µmol) and 10% palladium on carbon (9 mg) in ethanol (9 mL) under a hydrogen atmosphere at RT for 6 h, to provide the title compound (56 mg). LCMS (Method 15): 2.10 min, 800.3 $[M+H]^+$.

**Intermediate 944:** *N*-Ethyl-2-(6-methoxy-4-(trifluoromethyl)pyridin-3-yl)-*N*-methylethan-1-amine

**[001102]** A solution of **Intermediate 255** (1.16 g, 4.69 mmol) in TFA (5.8 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure then dissolved in DCM (14 mL). *N*-Methyl-ethylamine (81 mL, 9.38 mmol), triethylamine (1.18 mL, 8.45 mmol) and 4 Å molecular sieves were added and stirred at RT for 1 h. STAB (1.99 g, 9.38 mmol) was added and stirred at RT for 16 h. The mixture was filtered and filtrate concentrated under reduced pressure and purified by flash chromatography (25 g silica gel, eluting 0-20% (1 M ammonia MeOH) in DCM) to provide the title compound (0.95 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 8.17 (s, 1H), 6.96 (s, 1H), 3.95 (s, 3H), 2.91 – 2.83 (m, 2H), 2.62 – 2.46 (m, 4H), 2.32 (s, 3H), 1.08 (t, 3H).

**Intermediate 945:** 5-(2-(Ethyl(methyl)amino)ethyl)-4-(trifluoromethyl)pyridin-2(1*H*)-one

**[001103]** A solution of **Intermediate 944** (0.95 g, 3.62 mmol) in 33% HBr in AcOH (12.5 mL, 72.4 mmol) was stirred at 85 °C for 2 h. The mixture was cooled and concentrated under reduced pressure. The crude product was purified by catch and release chromatography (20 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.98 g). LCMS (Method 11): 1.20 min, 249.2 $[M+H]^+$.

**Intermediate 946:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[001104]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 638** (0.42 g, 0.60 mmol), **Intermediate 945** (0.16 g, 0.66 mmol) and $K_2CO_3$ (0.29 g, 1.80 mmol) in MeCN (8 mL) at reflux for 19 h. Purified by reverse phase chromatography (105 g C18, 40-50% MeCN in 0.1% aqueous formic acid) to provide the title compound (0.18 g). LCMS (Method 15): 2.91 min, 798.3 $[M+H]^+$.

**Intermediate 947:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001105]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 946** (0.18 g, 0.21 mmol) in DCE (0.10 L) and Grubbs II (19 mg, 22 µmol) at 50 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.14 g). LCMS (Method 11): 2.79 min, 770.6 $[M+H]^+$.

**Intermediate 948:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001106]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 947** (0.14 g, 0.18 mmol) and 10% palladium on carbon (19 mg) in ethanol (2 mL) under a hydrogen atmosphere at RT for 4.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-3% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.12 g). LCMS (Method 15): 2.10 min, 772.4 $[M+H]^+$.

**Intermediate 949:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[001107]** To a stirred suspension of **Intermediate 778** (6.39 g, 7.69 mmol) and Boc anhydride (2.01 g, 9.22 mmol) in DCM (77 mL) was added DIPEA (2.0 mL, 11.5 mmol) and the mixture stirred at RT for 18 h. The reaction mixture was diluted with DCM and washed with 1 M aqueous HCl, water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced

pressure. The crude product was purified by flash chromatography (80 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (6.50 g). LCMS (Method 15): 2.89 min, 416.2 $[M\text{-}Boc+H]^+$.

**Intermediate 950:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4,4'-difluoro-2'-(hex-4-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[001108]** A stirred solution of **Intermediate 949** (4.40 g, 8.53 mmol) in DMF (11.6 mL) was degassed then $Co(acac)_2$ (0.11 g, 0.43 mmol), $K_2CO_3$ (1.18 g, 8,53 mmol), Hantzch ester (2.16 g, 8,53 mmol, CAS 1149-23-1) and Xantphos (0.49 g, 0.85 mmol) were added and mixture stirred under 450 nm light irradiation for 4 days. The reaction mixture was diluted with EtOAc and washed with brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (80 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (3.40 g). LCMS (Method 22): 2.23 min, 416.2 $[M\text{-}Boc+H]^+$.

**Intermediate 951:** Ethyl (*S*)-3-amino-3-(4,4'-difluoro-2'-(hex-4-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001109]** A suspension of **Intermediate 950** (4.08 g, 7.91 mmol) in 4 M HCl in 1,4-dioxane (40 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (3.87 g). LCMS (Method 15): 2.67 min, 416.3 $[M+H]^+$.

**Intermediate 952:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-4-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxyhex-5-enamido)propanoate

**[001110]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 951** (4.60 g, 7.64 mmol), (2*R*)-2-hydroxyhex-5-enoic acid (1.19 g, 9.17 mmol, CAS 612825-60-2), DIPEA (3.99 mL, 22.9 mmol), HOBt (1.42 g, 8.40 mmol) and EDCI (1.78 g, 11.5 mmol) in MeCN (53 mL) at RT for 36 h. Purified by flash chromatography (40 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (2.24 g). LCMS (Method 15): 2.68 min, 528.3 $[M+H]^+$.

**Intermediate 953:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-4-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)hex-5-enamido)propanoate

**[001111]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 952** (1.50 g, 2.84 mmol), triethylamine (0.79 mL, 5.69 mmol) and methanesulfonyl chloride (0.33 mL, 4.26 mmol) in DCM (23 mL) at RT for 1 h, to provide the title compound (1.82 g). LCMS (Method 15): 2.71 min, 606.3 $[M+H]^+$.

**Intermediate 954:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)hex-5-enamido)-3-(4,4'-difluoro-2'-(hex-4-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[001112]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 953** (1.77 g, 2.75 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.73 g, 3.03 mmol, CAS 109919-32-6) and $K_2CO_3$ (1.14 g, 8.25 mmol) in MeCN (36 mL) at reflux for 18 h. Purified by flash chromatography (80 g silica gel, 0-30% EtOAc in petroleum ether) to provide the title compound (0.95 g). LCMS (Method 15): 2.92 min, 753.2 $[M+H]^+$.

**Intermediate 955:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-9-en-3-yl)acetate

**[001113]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 954** (0.95 g, 1.27 mmol) in DCE (0.53 L) and Grubbs II (0.11 g, 0.13 mmol) at 50 °C for 2.5 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.86 g). LCMS (Method 15): 2.78 min, 711.2 $[M+H]^+$.

**Intermediate 956:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-9-en-3-yl)acetate

**[001114]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 955** (0.19 g, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (13 mg, 19 μmol), copper(I) iodide (3.7 mg, 19 μmol), triethylamine (0.27 mL, 1.92 mmol) and *N*,*N*-dimethylpropargylamine (0.21 mL, 1.92 mmol, CAS 7223-38-3) in MeCN (3 mL) at 80 °C for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) then catch and release chromatography (2 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.13 g). LCMS (Method 15): 2.55 min, 712.3 $[M+H]^+$.

**Intermediate 957:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001115]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 956** (0.13 g, 0.18 mmol) and 10% palladium on carbon (19 mg) in ethanol (4 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 5-10% MeOH in DCM) to provide the title compound (0.10 g). LCMS (Method 15): 2.82 min, 718.4 $[M+H]^+$.

**Intermediate 958:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001116]** Prepared in an analogous manner to **Intermediate 748** using **Intermediate 747** (0.14 g, 0.12 mmol) in DCM (4.1 mL) and TFA (0.19 mL) at RT for 1 h, followed by DCM (14 mL). 3-fluoroazetidine hydrochloride (17 mg, 0.15 mmol, CAS 617718-46-4), triethylamine (52 µL, 0.37 mmol) and 4 Å molecular sieves at RT for 15 min, then STAB (53 mg, 0.25 mmol) at RT for 3 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (66 mg). LCMS (Method 15): 2.70 min, 786.3 $[M+H]^+$.

**Intermediate 959:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001117]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 958** (66 mg, 85 µmol) and 10% palladium on carbon (9 mg) in ethanol (9 mL) under a hydrogen atmosphere at RT for 14 h, to provide the title compound (55 mg). LCMS (Method 15): 2.69 min, 788.4 $[M+H]^+$.

**Intermediate 960:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-9-en-3-yl)acetate

**[001118]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 955** (0.62 g, 0.87 mmol), $Pd(PPh_3)_2Cl_2$ (61 mg, 87 µmol), copper(I) iodide (33 mg, 0.18 mmol), triethylamine (1.22 mL, 8.74 mmol) and *tert*-butyldimethyl-prop-2-ynoxy-silane (1.77 mL, 8.74 mmol, CAS 76782-82-6) in DMF (7 mL) at 110 °C for 5 h. Purified by flash chromatography (12 g silica gel, eluting 0-15% EtOAc in petroleum ether) to provide the title compound (0.53 g). LCMS (Method 15): 3.09 min, 799.4 $[M+H]^+$.

**Intermediate 961:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001119]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 960** (0.50 g, 0.60 mmol) and 10% palladium on carbon (64 mg) in ethanol (20 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.21 g). LCMS (Method 11): 3.11 min, 805.6 $[M+H]^+$.

**Intermediate 962:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(5-(3-hydroxypropyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001120]** Prepared in an analogous manner to **Intermediate 757** using **Intermediate 961** (0.13 g, 0.16 mmol) and TBAF (1 M in THF, 0.48 mL, 0.48 mmol) in THF (1.3 mL) at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-80% EtOAc in petroleum ether) to provide the title compound (55 mg). LCMS (Method 15): 2.54 min, 691.3 $[M+H]^+$.

**Intermediate 963:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001121]** Prepared in an analogous manner to **Intermediate 758** using **Intermediate 962** (50 mg, 72 µmol), triphenylphosphine (38 mg, 0.14 mmol), carbon tetrabromide (48 mg, 0.14 mmol) in DCM (1 mL) at RT for 2 h. Then azetidine (49 µL, 0.72 mmol) and $K_2CO_3$ (20 mg, 0.14 mmol) in MeCN (1 mL) at RT for 2 h. Purified by catch and release chromatography (2 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (41 mg). LCMS (Method 15): 2.85 min, 730.4 $[M+H]^+$.

**Intermediate 964:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-chloro-4,4',5,6'-tetrafluoro-[1,1'-biphenyl]-3-yl)propanoate

**[001122]** A solution of 2-bromo-1-chloro-3,5-difluorobenzene (1.67 g, 7.35 mmol, CAS 1020198-58-6), bis(pinacolato)diboron (2.11 g, 8.33 mmol) and potassium acetate (1.68 g, 17.1 mmol) in toluene (60 mL) and water (20 mL) was degassed with nitrogen. $Pd(dppf)Cl_2$ (0.41 g, 0.56 mmol) was added and the reaction mixture stirred at 110 °C for 20 h. The mixture was cooled, filtered through Celite® and concentrated under reduced pressure. The residue was dissolved in toluene (60 mL) then a degassed with nitrogen. **Intermediate 823** (2.0 g, 4.90 mmol), a solution of $K_3PO_4$ (3.64 g, 17.1 mmol) in water (20 mL) and XPhosPdG2 (0.19 g, 0.25 mmol) were added and the mixture was stirred at 110 °C for 7 h. The mixture was cooled and filtered through Celite®, washing with EtOAc and water. The organic layer was washed with brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (40 g silica gel, eluting 0-25% EtOAc in petroleum ether) to provide the title compound (1.85 g). LCMS (Method 15): 2.47 min, 376.0 $[M-Boc+H]^+$.

**Intermediate 965**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2',4,4',5-tetrafluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)propanoate

**[001123]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 964** (1.35 g, 2.83 mmol), 5-hexenylboronic acid (0.73 g, 5.67 mmol, CAS 1072952-16-9), $K_2CO_3$ (1.18 g, 8.51 mmol), palladium acetate (64 mg, 0.28 mmol) and SPhos (0.23 g, 0.57 mmol) in toluene (18 mL) and water (6 mL) at 85 °C for 1 h. Purified by flash chromatography (40 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (1.10 g). $^1H$

NMR (400 MHz; $CDCl_3$) δ: 6.99 – 6.94 (m, 2H), 6.80 (ddd, 1H), 6.70 (ddd, 1H), 5.81 – 5.64 (m, 2H), 5.37 (br s, 1H), 4.95 – 4.89 (m, 2H), 4.12 – 3.99 (m, 2H), 2.89 – 2.81 (m, 2H), 2.41 (t, 2H), 1.94 (dd, 2H), 1.44 – 1.37 (m, 11H), 1.30 – 1.22 (m, 2H), 1.17 (t, 3H).

**Intermediate 966:** Ethyl (*S*)-3-amino-3-(2',4,4',5-tetrafluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001124]** A suspension of **Intermediate 965** (1.10 g, 2.10 mmol) in 4 M HCl in 1,4-dioxane (7 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.97 g). LCMS (Method 11): 2.44 min, 424.3 $[M+H]^+$.

**Intermediate 967:** Ethyl (*S*)-3-((*R*)-2-hydroxypent-4-enamido)-3-(2',4,4',5-tetrafluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)propanoate

**[001125]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 966** (0.97 g, 2.11 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.26 g, 2.07 mmol, CAS 413622-10-3), DIPEA (0.74 mL, 4.14 mmol), HOBt (0.19 g, 1.38 mmol) and EDCI (0.32 g, 1.65 mmol) in MeCN (12 mL) at RT for 6 h. Purified by flash chromatography (40 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.48 g). LCMS (Method 21): 5.09 min, 522.2 $[M+H]^+$.

**Intermediate 968:** Ethyl (*S*)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)-3-(2',4,4',5-tetrafluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)propanoate

**[001126]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 967** (0.48 g, 0.92 mmol), triethylamine (0.26 mL, 1.84 mmol) and methanesulfonyl chloride (0.11 mL, 1.38 mmol) in DCM (5 mL) at 0 °C for 2.5 h, to provide the title compound (0.56 g). LCMS (Method 15): 2.53 min, 598.2 $[M-H]^-$.

**Intermediate 969:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(2',4,4',5-tetrafluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)propanoate

**[001127]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 968** (0.55 g, 0.92 mmol), **Intermediate 258** (0.26 g, 1.10 mmol) and $K_2CO_3$ (0.38 g, 2.75 mmol) in MeCN (41 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-5% (5% ammonia MeOH) in DCM) and again (25 g silica gel, eluting 0-5% (5% ammonia MeOH) in DCM) to provide the title compound (0.25 g). LCMS (Method 15): 2.68 min, 738.3 $[M+H]^+$.

**Intermediate 970:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$,$2^5$-tetrafluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001128]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 969** (0.25 g, 0.30 mmol) in DCE (0.11 L) and Grubbs II (26 mg, 30 µmol) at 40 °C for 6 h. Purified by flash chromatography (12 g silica gel, eluting 0-5% (0.5% ammonia in MeOH) in DCM) to provide the title compound (0.12 g). LCMS (Method 15): 2.57 min, 710.2 $[M+H]^+$; olefin isomerisation metathesis product: 2.49 min, 696.3 $[M-14+H]^+$.

**Intermediate 971:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$,$2^5$-tetrafluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001129]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 970** (0.12 g, 0.18 mmol) and 10% palladium on carbon (19 mg) in ethanol (5 mL) under a hydrogen atmosphere at RT for 2.5 h. Purified by flash chromatography (12 g silica gel, eluting 10% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.13 g). LCMS (Method 15): 2.50 min, 712.3 $[M+H]^+$; olefin isomerisation metathesis product: 2.77 min, 698.3 $[M-14+H]^+$.

**Intermediate 972:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[001130]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 638** (0.42 g, 0.60 mmol), **Intermediate 324** (0.17 g, 0.66 mmol) and $K_2CO_3$ (0.25 g, 1.80 mmol) in MeCN (8 mL) at reflux for 19 h. Purified by reverse phase chromatography (105 g C18, 40-50% MeCN in 0.1% aqueous formic acid) to provide the title compound (0.18 g). LCMS (Method 27): 2.87 min, 810.3 $[M+H]^+$.

**Intermediate 973:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-6-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001131]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 972** (0.18 g, 0.21 mmol) in DCE (0.11 L) and Grubbs II (19 mg, 22 µmol) at 50 °C for 5 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% (0.5% ammonia in MeOH) in DCM) to provide the title compound (0.15 g). LCMS (Method 27): 2.64 min, 782.3 $[M+H]^+$.

**Intermediate 974:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-6-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001132]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 973** (0.15 g, 0.19 mmol) and 10% palladium on carbon (20 mg) in ethanol (2 mL) under a hydrogen atmosphere at RT for 8 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% (0.5% ammonia MeOH) in DCM) to provide the title compound (92 mg). LCMS (Method 15): 2.88 min, 784.3 $[M+H]^+$.

**Intermediate 975:** Ethyl (*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enamido)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001133]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 636** (1.79 g, 2.55 mmol), *N*-Boc-(S)-allylglycine (0.66 g, 3.06 mmol, CAS 90600-20-7), DIPEA (1.33 mL, 7.64 mmol), HOBt (0.47 g, 2.80 mmol) and EDCI (0.59 g, 3.82 mmol) in MeCN (2 mL) at RT for 16 h. Additional EDCI (0.20 g, 1.27 mmol) and *N*-Boc-(S)-allylglycine (0.27 g, 1.27 mmol, CAS 90600-20-7) were added and stirred at RT for 2.5 h. Purified by flash chromatography (40 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (1.12 g). LCMS (Method 15): 2.78 min, 567.3 $[M-Boc+H]^+$.

**Intermediate 976:** Ethyl 2-((3*S*,6*S*)-6-((*tert*-butoxycarbonyl)amino)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001134]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 975** (0.55 g, 0.83 mmol) in DCE (0.37 L) and Grubbs II (63 mg, 70 µmol) at 50 °C for 1 h. Purified by flash chromatography (25 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.41 g). LCMS (Method 15): 2.67 min, 539.2 $[M-Boc+H]^+$.

**Intermediate 977:** Ethyl 2-((3*S*,6*S*)-6-((*tert*-butoxycarbonyl)amino)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001135]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 976** (0.91 g, 1.19 mmol) and 10% palladium on carbon (0.13 g) in ethanol (24 mL) under a hydrogen atmosphere at RT for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-5% MeOH in DCM) to provide the title compound (0.97 g). LCMS (Method 15): 2.72 min, 541.2 $[M-Boc+H]^+$.

**Intermediate 978:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-6-(3-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001136]** A solution of **Intermediate 977** (50 mg, 0.12 mmol) in 4 M HCl in 1,4-dioxane (0.39 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure then dissolved in DCE (2 mL) then methyl 2-(2-formylphenyl)acetate (20 mg, 0.11 mmol, CAS 63969-83-5), triethylamine (12 µL, 12 µmol) and STAB (19 mg, 89 µmol) were added and

stirred at RT for 1 h. Sodium borohydride (1 M in water, 50 µL, 50 µmol) was added and stirred at RT for 30 min. The mixture was diluted with DCM and washed with water. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (37 mg). LCMS (Method 15): 2.73 min, 671.1 $[M+H]^+$.

**Intermediate 979:** Ethyl (*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)hex-5-enamido)-3-(4,4'-difluoro-2'-(hex-4-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[001137]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 951** (0.43 g, 0.96 mmol), (2*S*)-2-(*tert*-butoxycarbonylamino)hex-5-enoic acid (0.26 g, 1.15 mmol, CAS 208522-13-8), DIPEA (0.50 mL, 2.87 mmol), HOBt (0.18 g, 1.05 mmol) and EDCI (0.22 g, 1.44 mmol) in MeCN (41 mL) at RT for 36 h. Purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.54 g). LCMS (Method 15): 2.80 min, 527.3 $[M\text{-Boc}+H]^+$.

**Intermediate 980:** Ethyl 2-((3*S*,6*S*)-6-((*tert*-butoxycarbonyl)amino)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-9-en-3-yl)acetate

**[001138]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 979** (0.54 g, 0.86 mmol) in DCE (0.43 L) and Grubbs II (73 mg, 86 µmol) at 50 °C for 2 h. Purified by flash chromatography (25 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.48 g). LCMS (Method 15): 2.63 min, 585.3 $[M+H]^+$.

**Intermediate 981:** Ethyl 2-((3*S*,6*S*)-6-((*tert*-butoxycarbonyl)amino)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001139]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 980** (0.48 g, 0.44 mmol) and 10% palladium on carbon (47 mg) in ethanol (16 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.44 g). LCMS (Method 15): 2.70 min, 587.3 $[M+H]^+$.

**Intermediate 982:** Ethyl 2-((3*S*,6*S*)-6-amino-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate hydrochloride

**[001140]** A suspension of **Intermediate 981** (0.30 g, 0.27 mmol) in 4 M HCl in 1,4-dioxane (0.33 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.24 g). LCMS (Method 15): 1.38 min, 487.2 $[M+H]^+$.

**Intermediate 983:** (*S*)-2-Hydroxy-5-methylhex-5-enoic acid

**[001141]** Prepared in an analogous manner to **Intermediate 925** using (2*R*)-2-amino-5-methyl-hex-5-enoic acid (1.60 g, 11.2 mmol, CAS 1369533-97-0) and sodium nitrite (1.54 g, 22.3 mmol) in AcOH (18 mL) and water (46 mL) at 0 °C for 1 h. Quenched with methylamine (2 M in THF, 11.4 mL) at 0 °C for 30 min. Purified by flash chromatography (80 g, silica, 0–10% MeOH in (1% AcOH in DCM)) to provide the title compound (0.74 g). $^1$H NMR (400 MHz; $CD_3OD$) δ: 4.73 (d, 2H), 4.11 (dd, 1H), 2.19 – 2.10 (m, 2H), 1.99 – 1.88 (m, 1H), 1.80 – 1.70 (m, 1H), 1.74 (s, 3H).

**Intermediate 984**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4,4'-difluoro-2'-hydroxy-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001142]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 346** (3.0 g, 6.55 mmol), **Intermediate 821** (2.48 g, 9.82 mmol), $K_3PO_4$ (4.17 g, 19.6 mmol), XPhosPdG2 (0.52 g, 0.66 mmol) in 1,4-dioxane (0.10 L) and water (18 mL) at 110 °C for 2 h. Purified by flash chromatography (80 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (3.36 g). LCMS (Method 22): 1.85 min, 502.2 $[M-H]^-$.

**Intermediate 985:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4,4'-difluoro-2'-methyl-5-(trifluoromethyl)-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[001143]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 984** (1.67 g, 3.02 mmol), phenyl triflimide (1.08 g, 3.02 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (1.18 g, 3.62 mmol) in DCM (15 mL) at RT for 16 h. Purified by flash chromatography (25 g silica gel, eluting 0–20% EtOAc in petroleum ether) to provide the title compound (1.95 g). LCMS (Method 22): 2.06 min, 634.2 $[M-H]^-$.

**Intermediate 986:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4,4'-difluoro-2'-methyl-6'-(pent-4-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001144]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 985** (1.01 g, 1.48 mmol), 4,4,5,5-tetramethyl-2-(pent-4-en-1-yl)-1,3,2-dioxaborolane (0.43 g, 2.21 mmol, CAS 157735-10-9), $K_2CO_3$ (0.61 g, 4.43 mmol), RuPhosPdG3 (0.12 g, 0.15 mmol) and RuPhos (69 mg, 0.15 mmol) in toluene (17 mL) and water (2 mL) at 95 °C for 1.5 h. Purified by flash chromatography (40 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (1.25 g). LCMS (Method 22): 2.17 min, 554.3 $[M-H]^-$.

**Intermediate 987:** Ethyl (*S*)-3-amino-3-(4,4'-difluoro-2'-methyl-6'-(pent-4-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001145]** A suspension of **Intermediate 986** (0.88 g, 1.44 mmol) in 4 M HCl in 1,4-dioxane (3.6 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure to provide the title compound (0.85 g). LCMS (Method 22): 2.04 min, 456.2 $[M+H]^+$.

**Intermediate 988:** Ethyl (*S*)-3-(4,4'-difluoro-2'-methyl-6'-(pent-4-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxy-5-methylhex-5-enamido)propanoate

**[001146]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 987** (0.71 g, 1.44 mmol), **Intermediate 983** (0.31 g, 2.15 mmol), DIPEA (1.0 mL, 5.74 mmol), HOBt (0.21 g, 1.58 mmol) and EDCI (0.41 g, 2.15 mmol) in MeCN (13 mL) at RT for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.73 g). LCMS (Method 22): 2.68 min, 582.3 $[M+H]^+$.

**Intermediate 989:** Ethyl (*S*)-3-(4,4'-difluoro-2'-methyl-6'-(pent-4-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-5-methyl-2-((methylsulfonyl)oxy)hex-5-enamido)propanoate

**[001147]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 988** (0.40 g, 0.61 mmol), triethylamine (0.17 mL, 1.21 mmol) and methanesulfonyl chloride (70 µL, 0.91 mmol) in DCM (4.2 mL) at RT for 1 h, to provide the title compound (0.51 g). LCMS (Method 15): 2.68 min, 660.2 $[M+H]^+$.

**Intermediate 990:** Ethyl (*S*)-3-(4,4'-difluoro-2'-methyl-6'-(pent-4-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-methylhex-5-enamido)propanoate

**[001148]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 989** (0.46 g, 0.70 mmol), **Intermediate 258** (0.25 g, 1.05 mmol) and $K_2CO_3$ (0.29 g, 2.11 mmol) in MeCN (6 mL) at reflux for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.36 g). LCMS (Method 15): 2.84 min, 798.4 $[M+H]^+$.

**Intermediate 991:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,9-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-9-en-3-yl)acetate

**[001149]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 990** (0.36 g, 0.45 mmol) in DCE (0.15 L) and Grubbs II (38 mg, 45 µmol) at 50 °C for 2 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.25 g). LCMS (Method 15): 2.76 min, 770.3 $[M+H]^+$.

**Intermediate 992:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,9-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001150]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 991** (0.25 g, 0.33 mmol) and 10% palladium on carbon (35 mg) in ethanol (11 mL) under a hydrogen atmosphere at RT for 96 h. Purified by flash chromatography (25 g silica gel, eluting

0-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.14 g). LCMS (Method 15): 2.82 and 2.83 min, 772.5 $[M+H]^+$.

**Intermediate 993**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-chloro-4,4',6'-trifluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001151]** Prepared in an analogous manner to **Intermediate 964** using 2-bromo-1-chloro-3,5-difluorobenzene (0.74 g, 3.27 mmol, CAS 1020198-58-6), potassium acetate (0.75 g, 7.64 mmol), bis(pinacolato)diboron (0.95 g, 3.74 mmol) and $Pd(dppf)Cl_2$ (80 mg, 0.11 mmol) in toluene (27 mL) at 110 °C for 2.5 h. Then with **Intermediate 346** (1.0 g, 2.18 mmol), $K_3PO_4$ (1.62 g, 3.50 mmol) and XPhosPdG2 (86 mg, 0.11 mmol) in water (9 mL) and toluene (27 mL) at 110 °C for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-15% EtOAc in petroleum ether) to provide the title compound (0.45 g). LCMS (Method 15): 2.55 min, 524.1 $[M-H]^-$.

**Intermediate 994**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001152]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 993** (0.91 g, 1.73 mmol), 5-hexenylboronic acid (0.37 g, 2.91 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.72 g, 2.99 mmol), palladium acetate (43 mg, 0.19 mmol) and SPhos (0.15 g, 0.35 mmol) in toluene (25 mL) and water (6 mL) at 90 °C for 2.5 h. Purified by flash chromatography (40 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.63 g). $^1H$ NMR (400 MHz; $CDCl_3$) δ: 7.45 (dd, 1H), 7.38 (d, 1H), 6.83 (d, 1H), 6.76 – 6.69 (m, 1H), 5.88 – 5.60 (m, 2H), 5.48 – 5.33 (m, 1H), 4.96 – 4.74 (m, 2H), 4.13 – 3.96 (m, 2H), 2.97 – 2.82 (m, 2H), 2.45 – 2.33 (m, 2H), 1.97 – 1.86 (m, 2H), 1.47 – 1.31 (m, 11H), 1.30 – 1.22 (m, 2H), 1.17 (t, 3H).

**Intermediate 995:** Ethyl (*S*)-3-amino-3-(2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001153]** A suspension of **Intermediate 994** (0.71 g, 1.23 mmol) in 4 M HCl in 1,4-dioxane (3 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (0.67 g). LCMS (Method 15): 2.62 min, 474.1 $[M+H]^+$.

**Intermediate 996:** Ethyl (*S*)-3-((*R*)-2-hydroxypent-4-enamido)-3-(2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001154]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 995** (0.67 g, 1.12 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.22 g, 1.68 mmol, CAS 413622-10-3), DIPEA (0.58 mL, 3.35 mmol), HOBt (0.21 g, 1.23 mmol) and EDCI (0.26 g, 1.68 mmol) in MeCN (16 mL) at RT for 16 h. Additional (2*R*)-2-hydroxypent-4-enoic acid (72 mg, 0.56 mmol)

and EDCI (43 mg, 0.28 mmol) added and stirred at RT for 4 h. Purified by flash chromatography (25 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.40 g). LCMS (Method 15): 2.58 min, 572.2 $[M+H]^+$.

**Intermediate 997:** Ethyl (*S*)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)-3-(2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001155]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 996** (0.40 g, 0.59 mmol), triethylamine (0.24 mL, 1.77 mmol) and methanesulfonyl chloride (91 µL, 1.18 mmol) in DCM (6 mL) at RT for 2 h, to provide the title compound (0.51 g). LCMS (Method 15): 2.63 min, 648.2 $[M-H]^-$.

**Intermediate 998:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001156]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 997** (0.51 g, 0.92 mmol), **Intermediate 258** (0.22 g, 0.92 mmol) and $K_2CO_3$ (0.25 g, 1.84 mmol) in MeCN (6 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-5% MeOH in DCM) to provide the title compound (0.27 g). LCMS (Method 15): 2.77 min, 788.3 $[M+H]^+$.

**Intermediate 999:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$-trifluoro-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001157]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 998** (0.27 g, 0.29 mmol) in DCE (0.17 L) and Grubbs II (24 mg, 29 µmol) at 50 °C for 2 h. Purified by flash chromatography (25 g silica gel, eluting 0-5% MeOH in DCM) to provide the title compound (0.25 g). LCMS (Method 15): 2.66 min, 760.3 $[M+H]^+$.

**Intermediate 1000:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$-trifluoro-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001158]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 999** (0.25 g, 0.17 mmol) and 10% palladium on carbon (25 mg) in ethanol (25 mL) under a hydrogen atmosphere at RT for 8 h. Purified by flash chromatography (25 g silica gel, eluting 0-5% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.17 g). LCMS (Method 15): 2.69 min, 762.3 $[M+H]^+$.

**Intermediate 1001:** Ethyl (*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enamido)-3-(4,4',5-trifluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001159]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 827** (1.38 g, 2.36 mmol), *N*-Boc-(S)-allylglycine (0.76 g, 3.54 mmol, CAS 90600-20-7), DIPEA (1.23 mL, 7.08 mmol), HOBt (0.44 g, 2.60 mmol) and EDCI (0.55 g, 3.54 mmol) in MeCN (19 mL) at RT for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (1.43 g). LCMS (Method 15): 2.71 min, 615.3 $[M-H]^-$.

**Intermediate 1002:** Ethyl 2-((3*S*,6*S*)-6-((*tert*-butoxycarbonyl)amino)-$1^4$,$2^4$,$2^5$-trifluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001160]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1001** (1.43 g, 2.18 mmol) in DCE (0.73 L) and Grubbs II (0.19 g, 0.22 mmol) at 50 °C for 2 h. Purified by flash chromatography (25 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (1.1 g). LCMS (Method 15): 2.63 min, 587.3 $[M-H]^-$.

**Intermediate 1003:** Ethyl 2-((3*S*,6*S*)-6-((*tert*-butoxycarbonyl)amino)-$1^4$,$2^4$,$2^5$-trifluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001161]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1002** (1.10 g, 1.87 mmol) and 10% palladium on carbon (0.20 g) in ethanol (37 mL) under a hydrogen atmosphere at RT for 2 h. Purified by flash chromatography (40 g silica gel, eluting 0-5% MeOH in DCM) to provide the title compound (0.98 g). LCMS (Method 15): 2.65 min, 589.3 $[M-H]^-$.

**Intermediate 1004:** Ethyl 2-((3*S*,6*S*)-6-amino-$1^4$,$2^4$,$2^5$-trifluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate hydrochloride

**[001162]** A suspension of **Intermediate 1003** (0.30 g, 0.51 mmol) in 4 M HCl in 1,4-dioxane (0.6 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.32 g). LCMS (Method 15): 2.32 min, 491.2 $[M+H]^+$.

**Intermediate 1005:** Ethyl 4-(((10*S*,13*S*)-13-(2-ethoxy-2-oxoethyl)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-10-yl)amino)-3,3-dimethylbutanoate

**[001163]** Prepared in an analogous manner to **Intermediate 940** using **Intermediate 853** (0.18 g, 0.34 mmol), triethylamine (0.24 mL, 1.71 mmol) and ethyl 3,3-dimethyl-4-oxo-butanoate (0.11 g, 0.34 mmol, CAS 50891-56-0) in EtOAc (5.4 mL) and IPA (1.8 mL) for 15 min, then STAB (0.36 g, 1.71 mmol) was added and the mixture stirred at RT for 3 h, to provide the title compound (0.29 g). LCMS (Method 15): 2.60 min, 631.4 $[M+H]^+$.

**Intermediate 1006:** Ethyl 2-((10*S*,13*S*)-10-(4,4-dimethyl-2-oxopyrrolidin-1-yl)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[001164]** A solution of **Intermediate 1005** (0.22 g, 0.34 mmol) in MeCN (41 mL) and AcOH (59 µL, 1.03 mmol) was stirred at 50 °C for 16 h. The mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography (24 g silica gel, eluting 10-60% EtOAc in petroleum ether) to provide the title compound (0.11 g). LCMS (Method 15): 2.42 min, 585.5 $[M+H]^+$.

**Intermediate 1007:** Ethyl 2-((3*S*,6*S*)-6-amino-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate hydrochloride

**[001165]** A suspension of **Intermediate 977** (0.10 g, 0.16 mmol) in 4 M HCl in 1,4-dioxane (1.4 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.13 g). LCMS (Method 22): 1.90 min, 541.3 $[M+H]^+$.

**Intermediate 1008:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-6-(3-oxo-2-azaspiro[4.4]nonan-2-yl)-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001166]** Prepared in an analogous manner to **Intermediate 940** using **Intermediate 1007** (90 mg, 0.16 mmol), triethylamine (43 µL, 0.31 mmol) and ethyl 2-(1-formylcyclopentyl)acetate (57 mg, 0.31 mmol, CAS 73739-60-3) in DCE (3 mL) and STAB (66 mg, 0.31 mmol) at RT for 18 h. Additional ethyl 2-(1-formylcyclopentyl)acetate (14 mg, 78 µmol) and STAB (17 mg, 78 µmol) were added and stirred at RT for 30 h. After work up, the residue was dissolved in MeCN (5 mL) and AcOH (27 µL) and heated at 75 °C for 2.5 h, then the volatiles were removed under reduced pressure. Purified by flash chromatography (25 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (88 mg). LCMS (Method 15): 2.15 min, 663.3 $[M+H]^+$.

**Intermediate 1009:** Ethyl (*S*)-3-((*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enamido)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001167]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 506** (1.15 g, 1.68 mmol), *N*-Boc-(S)-allylglycine (0.58 g, 2.69 mmol, CAS 90600-20-7), DIPEA (1.17 mL, 6.73 mmol), HOBt (0.34 g, 2.52 mmol) and EDCI (0.55 g, 2.86 mmol) in MeCN (12 mL) at RT for 24 h. Purified by flash chromatography (24 g silica gel, eluting 0-25% EtOAc in petroleum ether) to provide the title compound (0.58 g). LCMS (Method 22): 2.19 min, 637.4 $[M-H]^-$.

**Intermediate 1010:** Ethyl 2-((3*S*,6*S*)-6-((*tert*-butoxycarbonyl)amino)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001168]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1009** (0.58 g, 0.77 mmol) in DCE (0.11 L) and Grubbs II (66 mg, 77 µmol) at 50 °C for 2 h. Purified

by flash chromatography (25 g silica gel, eluting 0-35% EtOAc in petroleum ether) to provide the title compound (0.33 g). LCMS (Method 15): 2.13 min, 611.4 $[M+H]^+$.

**Intermediate 1011:** Ethyl 2-((3*S*,6*S*)-6-((*tert*-butoxycarbonyl)amino)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001169]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1010** (0.33 g, 0.48 mmol) and 10% palladium on carbon (25 mg) in ethanol (12 mL) under a hydrogen atmosphere at RT for 4 h. Purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.31 g). LCMS (Method 22): 2.13 min, 613.4 $[M+H]^+$.

**Intermediate 1012:** *tert*-Butyl 4-(2-ethoxy-2-oxoethyl)-4-formylpiperidine-1-carboxylate

**[001170]** To a stirred solution of *tert*-butyl 4-formylpiperidine-1-carboxylate (5.0 g, 23.4 mmol, CAS 137076-22-3) in toluene (50 mL) was added diisobutylamine (4.50 mL, 25.8 mmol) and the mixture was heated at reflux for 18 h with a Dean-Stark trap. The volatiles were removed and then residue dissolved in MeCN (50 mL) followed by addition of ethyl bromoacetate (3.12 mL, 28.1 mmol) and the mixture was stirred at 90 °C for 16 h. The mixture was diluted with 10% aqueous citric acid and extracted with diethyl ether. The organic layer was washed with water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (80 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (1.31 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 9.66 (s, 1H), 4.11 (q, 2H), 3.99 (s, 2H), 3.63 (d, 2H), 3.25 – 3.18 (m, 2H), 2.57 (s, 2H), 2.01 – 1.84 (m, 2H), 1.45 (s, 9H), 1.23 (t, 3H).

**Intermediate 1013:** *tert*-Butyl 1-hydroxy-3-oxo-2-oxa-8-azaspiro[4.5]decane-8-carboxylate

**[001171]** To a stirred solution of **Intermediate 1012** (0.20 g, 0.27 mmol) in THF (1 mL) and water (0.2 mL) was added lithium hydroxide (13 mg, 0.53 mmol) and the mixture was stirred at RT for 2 h. The mixture was diluted with aqueous $NaHCO_3$ and extracted with EtOAc. The aqueous layer was acidified with 2 M aqueous HCl and extracted with EtOAc. The organic layer washed with brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (0.10 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 5.50 (s, 1H), 4.04 – 3.96 (m, 1H), 3.68 – 3.55 (m, 2H), 3.32 – 3.19 (m, 1H), 3.21 – 3.10 (m, 1H), 2.85 (t, 1H), 2.57 (d, 1H), 2.37 (d, 1H), 1.85 – 1.75 (m, 1H), 1.72 – 1.54 (m, 2H), 1.44 (s, 9H).

**Intermediate 1014:** Ethyl 2-((3*S*,6*S*)-6-amino-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate hydrochloride

**[001172]** A suspension of **Intermediate 1011** (0.25 g, 0.38 mmol) in 4 M HCl in 1,4-dioxane (1.4 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.21 g). LCMS (Method 22): 1.92 min, 513.3 $[M+H]^+$.

**Intermediate 1015:** *tert*-Butyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-3-(2-ethoxy-2-oxoethyl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-6-yl)-3-oxo-2,8-diazaspiro[4.5]decane-8-carboxylate

**[001173]** Prepared in an analogous manner to **Intermediate 940** using **Intermediate 1014** (0.21 g, 0.38 mmol), triethylamine (0.16 mL, 1.15 mmol) and **Intermediate 1013** (0.18 g, 0.46 mmol) in DCM (8 mL) at RT for 30 min, then STAB (0.16 g, 0.77 mmol) at RT for 64 h. After work up, the residue was dissolved in MeCN (4 mL) and AcOH (0.22 mL) and heated at 75 °C for 18 h, then the volatiles were removed under reduced pressure, to provide the title compound (0.31 g). LCMS (Method 22): 2.14 min, 750.4 $[M+H]^+$.

**Intermediate 1016:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-6-(3-oxo-2,8-diazaspiro[4.5]decan-2-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001174]** A solution of **Intermediate 1015** (0.31 g, 0.41 mmol) in DCM (3 mL) and TFA (0.31 mL) was stirred at RT for 4 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with DCM. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (0.16 g). LCMS (Method 18): 1.67 min, 650.4 $[M+H]^+$.

**Intermediate 1017:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-6-(8-methyl-3-oxo-2,8-diazaspiro[4.5]decan-2-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001175]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 1016** (0.11 g, 0.17 mmol), formaldehyde (37% in water, 0.92 mL, 33.9 mmol), triethylamine (0.10 mL, 0.75 mmol) in MeOH (2 mL) at RT for 30 min, then STAB (99 mg, 0.47 mmol) at RT for 4 h, to provide the title compound (50 mg). LCMS (Method 12): 2.05 min, 662.8 $[M-H]^-$.

**Intermediate 1018:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001176]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 638** (0.50 g, 0.62 mmol), 5-bromo-3-fluoro-1*H*-pyridin-2-one (0.18 g, 0.94 mmol, CAS 156772-63-3) and $K_2CO_3$ (0.26 g, 1.87 mmol) in MeCN (15 mL) at reflux for 17 h. Purified by flash chromatography (40 g silica gel, 0-40% EtOAc in petroleum ether) to provide the title compound (0.26 g). LCMS (Method 15): 2.76 min, 743.2 $[M+H]^+$.

**Intermediate 1019:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001177]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1018** (0.26 g, 0.32 mmol) in DCE (0.16 L) and Grubbs II (27 mg, 32 µmol) at 50 °C for 2 h. Purified by flash chromatography (25 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.21 g). LCMS (Method 15): 2.67 min, 713.4 $[M-H]^-$.

**Intermediate 1020:** Ethyl 2-((3*S*,6*S*)-6-(5-((*E*)-2-ethoxyvinyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001178]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 1019** (0.21 g, 0.24 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (56 mg, 0.28 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (17 mg, 24 µmol) and $Na_2CO_3$ (50 mg, 0.47 mmol) in 1,4-dioxane (8 mL) and water (2.5 mL) at 85 °C for 2 h. Purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether), to provide the title compound (0.11 g). LCMS (Method 15): 2.72 min, 705.3 $[M+H]^+$.

**Intermediate 1021:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001179]** Prepared in an analogous manner to **Intermediate 748**, using **Intermediate 1020** (0.11 g, 0.14 mmol) in DCM (5 mL) and TFA (0.21 mL) at RT for 1 h, then 3-fluoroazetidine hydrochloride (15 mg, 0.14 mmol, CAS 617718-46-4), triethylamine (96 µL, 0.69 mmol) in DCM ( 5 mL) and 4 Å molecular sieves at RT for 30 min, followed by STAB (59 mg, 0.28 mmol) at RT for 16 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (25 mg). LCMS (Method 15): 2.59 min, 736.3 $[M+H]^+$.

**Intermediate 1022:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001180]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1021** (25 mg, 28 µmol) and 10% palladium on carbon (6 mg) in ethanol (5 mL) under a hydrogen atmosphere at RT for 6 h, to provide the title compound (20 mg). LCMS (Method 15): 2.65 min, 738.4 $[M+H]^+$.

**Intermediate 1023:** Ethyl 2-((3*S*,6*S*)-6-(5-((*E*)-2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-9-en-3-yl)acetate

**[001181]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 955** (0.15 g, 0.21 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (43 mg, 0.22 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (15 mg, 21 μmol) and $Na_2CO_3$ (44 mg, 0.41 mmol) in 1,4-dioxane (2.6 mL) and water (0.7 mL) at 85 °C for 3 h. Conditions repeated. Purified by flash chromatography (12 g silica gel, eluting 0-60% EtOAc in petroleum ether), to provide the title compound (64 mg). LCMS (Method 15): 2.79 min, 701.3 $[M+H]^+$.

**Intermediate 1024:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-9-en-3-yl)acetate

**[001182]** Prepared in an analogous manner to **Intermediate 748**, using **Intermediate 1023** (0.11 g, 0.14 mmol) in DCM (1.2 mL) and TFA (0.14 mL) at RT for 2 h, then 3-methoxyazetidine hydrochloride (14 mg, 0.11 mmol, CAS 148644-09-1), triethylamine (52 μL, 0.37 mmol) in DCM (4 mL) and 4 Å molecular sieves at RT for 15 min, followed by STAB (39 mg, 0.19 mmol) at RT for 2 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (31 mg). LCMS (Method 15): 2.70 min, 744.3 $[M+H]^+$.

**Intermediate 1025:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001183]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1024** (31 mg, 42 μmol) and 10% palladium on carbon (4.4 mg) in ethanol (3.7 mL) under a hydrogen atmosphere at RT for 3 h, to provide the title compound (26 mg). LCMS (Method 15): 2.74 min, 746.3 $[M+H]^+$.

**Intermediate 1026:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001184]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 746** (50 mg, 61 μmol) and 10% palladium on carbon (6.5 mg) in EtOAc (3.7 mL) under a hydrogen atmosphere at RT for 6 h. Purified by flash chromatography (12 g silica gel, eluting 50-100% EtOAc in petroleum ether) to provide the title compound (28 mg). LCMS (Method 21): 6.13 min, 765.1 $[M+H]^+$.

**Intermediate 1027:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(4,4',5-trifluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001185]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 829** (0.44 g, 0.67 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.18 g, 0.74 mmol, CAS 109919-32-6) and $K_2CO_3$ (0.28 g, 2.02 mmol) in MeCN (8 mL) at reflux for 18 h. Purified by flash chromatography (25 g silica gel, 0-40% EtOAc in petroleum ether) to provide the title compound (0.21 g). LCMS (Method 11): 2.72 min, 741.3 $[M+H]^+$.

**Intermediate 1028:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$,$2^5$-trifluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001186]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1027** (0.21 g, 0.27 mmol) in DCE (0.13 L) and Grubbs II (23 mg, 27 µmol) at 50 °C for 3 h. Purified by flash chromatography (25 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.17 g). LCMS (Method 15): 2.75 min, 715.4 $[M+H]^+$.

**Intermediate 1029:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$,$2^5$-trifluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001187]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 1028** (0.17 g, 0.24 mmol), $Pd(PPh_3)_2Cl_2$ (21 mg, 29 µmol), copper(I) iodide (3.2 mg, 17 µmol), triethylamine (0.36 mL, 2.55 mmol) and *N,N*-dimethylpropargylamine (0.27 mL, 2.55 mmol, CAS 7223-38-3) in MeCN (3 mL) at 80 °C for 48 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (93 mg). LCMS (Method 15): 2.65 min, 716.3 $[M+H]^+$.

**Intermediate 1030:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$,$2^5$-trifluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001188]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1029** (92 mg, 0.13 mmol) and 10% palladium on carbon (13.5 mg) in ethanol (13 mL) under a hydrogen atmosphere at RT for 7 h. Conditions repeated for 3 h. Purified by catch and release chromatography (SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (74 mg). LCMS (Method 15): 2.84 min, 722.4 $[M+H]^+$.

**Intermediate 1031:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001189]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 638** (0.56 g, 0.70 mmol), 5-bromo-1*H*-pyridin-2-one (0.13 g, 0.76 mmol, CAS 13466-38-1) and $K_2CO_3$ (0.29 g, 2.09 mmol) in MeCN (8 mL) at reflux for 18 h. Purified by flash chromatography (25 g silica gel, 0-50% EtOAc in petroleum ether) to provide the title compound (0.20 g). LCMS (Method 15): 2.78 min, 725.2 $[M+H]^+$.

**Intermediate 1032:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001190]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1031** (0.24 g, 0.33 mmol) in DCE (0.17 L) and Grubbs II (28 mg, 33 µmol) at 50 °C for 3 h. Purified by flash chromatography (25 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (0.17 g). LCMS (Method 15): 2.69 min, 697.3 $[M+H]^+$.

**Intermediate 1033:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001191]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 1032** (0.17 g, 0.23 mmol), $Pd(PPh_3)_2Cl_2$ (22 mg, 32 µmol), copper(I) iodide (3.1 mg, 16 µmol), triethylamine (0.42 mL, 3.26 mmol) and *N,N*-dimethylpropargylamine (0.36 mL, 3.26 mmol, CAS 7223-38-3) in MeCN (3 mL) at 80 °C for 24 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) then catch and release chromatography (SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.10 g). LCMS (Method 15): 2.61 min, 698.3 $[M+H]^+$.

**Intermediate 1034:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(dimethylamino)propyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001192]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1033** (0.10 g, 0.14 mmol) and 10% palladium on carbon (15 mg) in ethanol (13 mL) under a hydrogen atmosphere at RT for 7 h. Conditions repeated for 3 h. Purified by catch and release chromatography (SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (71 mg). LCMS (Method 15): 2.77 min, 704.3 $[M+H]^+$.

**Intermediate 1035:** Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-methyl-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[001193]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 3** (1.30 g, 3.04 mmol), phenyl triflimide (1.30 g, 3.65 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (1.20 g, 3.67 mmol) in DCM (25 mL) at RT for 16 h. Purified by flash chromatography (40 g silica

gel, eluting 0–40% EtOAc in petroleum ether) to provide the title compound (1.40 g). LCMS (Method 15): 2.35 min, 516.2 $[M-H]^-$.

**Intermediate 1036:** Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001194]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 1035** (1.23 g, 2.38 mmol), 5-hexenylboronic acid (0.45 g, 3.55 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.98 g, 2.99 mmol), palladium acetate (51 mg, 0.23 mmol) and RuPhos (0.15 g, 0.31 mmol) in toluene (44 mL) and water (11 mL) at 90 °C for 1 h. Purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.72 g). LCMS (Method 15): 2.69 min, 352.2 $[M-Boc+H]^+$.

**Intermediate 1037:** Methyl (*S*)-3-amino-3-(2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001195]** A suspension of **Intermediate 1036** (0.85 g, 1.88 mmol) in 4 M HCl in 1,4-dioxane (4 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to provide the title compound (0.73 g). LCMS (Method 15): 2.45 min, 352.2 $[M+H]^+$.

**Intermediate 1038:** Methyl (*S*)-3-(2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[001196]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 1037** (0.73 g, 1.88 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.35 g, 3.01 mmol, CAS 413622-10-3), DIPEA (1.04 mL, 5.76 mmol), HOBt (0.25 g, 1.88 mmol) and EDCI (0.43 g, 2.26 mmol) in MeCN (14 mL) at RT for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.48 g). LCMS (Method 15): 2.44 min, 450.2 $[M+H]^+$.

**Intermediate 1039:** Methyl (*S*)-3-(2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[001197]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 1038** (0.48 g, 0.94 mmol), triethylamine (0.26 mL, 1.89 mmol) and methanesulfonyl chloride (0.11 mL, 1.42 mmol) in DCM (8 mL) at RT for 1.5 h, to provide the title compound (0.50 g). LCMS (Method 15): 2.58 min, 528.2 $[M+H]^+$.

**Intermediate 1040:** Methyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001198]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 1039** (0.50 g, 0.94 mmol), **Intermediate 137** (0.16 g, 0.94 mmol) and $K_2CO_3$ (0.39 g, 2.83

mmol) in MeCN (12 mL) at 80 °C for 18 h. Purified by flash chromatography (24 g silica gel, eluting 2-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.16 g). LCMS (Method 15): 2.59 min, 598.4 $[M+H]^+$.

**Intermediate 1041:** Methyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001199]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1040** (0.16 g, 0.27 mmol) in DCE (71 mL) and Grubbs II (23 mg, 27 µmol) at 40 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 2-10% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.15 g). LCMS (Method 15): 2.42 min, 570.3 $[M+H]^+$.

**Intermediate 1042:** Methyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001200]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1041** (0.15 g, 0.27 mmol) and 10% palladium on carbon (28 mg) in ethanol (5 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 2-10% (0.1% ammonia MeOH) in DCM) to provide the title compound (85 mg). LCMS (Method 15): 2.47 min, 572.3 $[M+H]^+$.

**Intermediate 1043:** Ethyl 2-(4-formyltetrahydro-2*H*-pyran-4-yl)acetate

**[001201]** To a stirred solution of ethyl 2-(4-vinyltetrahydropyran-4-yl)acetate (1.06 g, 5.35 mmol, CAS 252722-04-6) in MeCN (17 mL) and water (8.3 mL) was added osmium tetroxide (4% dispersion in water, 1.70 mL, 0.27 mmol) and sodium periodate (2.63 g, 12 3 mmol) then the mixture was stirred at RT for 16 h. The mixture was diluted with aqueous sodium thiosulfate then stirred at RT for 15 min. The mixture was extracted with diethyl ether. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (24 g silica gel, eluting 20-60% diethyl ether in petroleum ether) to provide the title compound (0.41 g). $^1H$ NMR (400 MHz; $CDCl_3$) δ: 9.72 (s, 1H), 4.14 (q, 2H), 3.82 – 3.77 (m, 2H), 3.64 – 3.58 (m, 2H), 2.63 (s, 2H), 2.06 – 2.00 (m, 2H), 1.69 – 1.62 (m, 2H), 1.26 (t, 3H).

**Intermediate 1044:** Ethyl 2-(4-((*E*)-(((3*S*,6*S*)-3-(2-ethoxy-2-oxoethyl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-6-yl)imino)methyl)tetrahydro-2*H*-pyran-4-yl)acetate

**[001202]** To a solution of **Intermediate 1007** (0.15 g, 0.27 mmol) in EtOAc (4.5 mL) and IPA (1.5 mL) was added triethylamine (0.19 mL, 1.33 mmol) and **Intermediate 1043** (71 mg, 0.27 mmol) in EtOAc (2.3 mL) and IPA (0.8 mL) at RT and stirred for 15 min. STAB (0.28 g, 1.33 mmol) was added and the mixture stirred at RT for 3 h. The mixture was diluted with

water and extracted with EtOAc. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (0.22 g). LCMS (Method 15): 2.76 min, 723.3 $[M+H]^+$.

**Intermediate 1045:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-6-(3-oxo-8-oxa-2-azaspiro[4.5]decan-2-yl)-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001203]** A solution of **Intermediate 1044** (0.19 g, 0.27 mmol) in MeCN (19 mL) and AcOH (46 µL, 1.03 mmol) was stirred at 50 °C for 2.5 h. STAB (56 mg, 0.27 mmol) was added and heated at 50 °C for 1 h. The mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography (24 g silica gel, eluting 20-70% EtOAc in petroleum ether) to provide the title compound (85 mg). LCMS (Method 15): 2.64 min, 679.3 $[M+H]^+$.

**Intermediate 1046:** 3-Ethyl-5-fluoro-2-iodophenol

**[001204]** Prepared in an analogous manner to **Intermediate 759** using 3-ethyl-5-fluorophenol (0.37 g, 2.43 mmol, CAS 1243390-46-6), sodium hydride (60% dispersion in oil, 0.20 g, 4.90 mmol) in toluene (13 mL) at 0 °C for 30 min then iodine (0.62 g, 2.43 mmol) added portion wise over 30 min at RT. Purified by flash chromatography (12 g silica gel, eluting 0-5% EtOAc in petroleum ether) to provide the title compound (0.19 g). LCMS (Method 15): 1.17 min, 264.9 $[M-H]^-$.

**Intermediate 1047:** 1-Ethyl-5-fluoro-2-iodo-3-(methoxymethoxy)benzene

**[001205]** To a solution of **Intermediate 1046** (2.80 g, 8.0 mmol) in DCM (45 mL) at RT was added DIPEA (3.48 mL, 20.0 mmol) and chloromethyl methyl ether (0.73 mL, 9.60 mmol) then stirred at RT for 20 h. The mixture was washed with water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (80 g silica gel, eluting 0-5% EtOAc in petroleum ether) to provide the title compound (0.99 g). $^1H$ NMR (400 MHz; $CDCl_3$) δ: 6.70 (dd, 2H), 5.22 (s, 2H), 3.51 (s, 3H), 2.78 (q, 2H), 1.20 (t, 3H).

**Intermediate 1048:** 2-(2-Ethyl-4-fluoro-6-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

**[001206]** Prepared in an analogous manner to **Intermediate 2** using **Intermediate 1047** (0.99 g, 3.19 mmol), bis(pinacolato)diboron (0.97 g, 3.83 mmol), $Cs_2CO_3$ (1.56 g, 4.80 mmol), tris(4-methoxyphenyl)phosphine (61 mg, 0.18 mmol) and palladium acetate (36 mg, 0.16 mmol) in EtOAc (17 mL) at 80 °C for 4 h. Purified by flash chromatography (24 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.50 g). $^1H$ NMR (400

MHz; $CDCl_3$) δ: 6.61 – 6.52 (m, 2H), 5.11 (s, 2H), 3.46 (s, 3H), 2.62 (q, 2H), 1.38 (s, 12H), 1.20 (t, 3H).

**Intermediate 1049:** 3-Ethyl-5-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

**[001207]** A suspension of **Intermediate 1048** (0.63 g, 1.93 mmol) in 4 M HCl in 1,4-dioxane (2.4 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.52 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 8.82 (s, 1H), 6.49 – 6.36 (m, 2H), 2.87 (q, 2H), 1.36 (s, 12H), 1.15 (t, 3H).

**Intermediate 1050**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-ethyl-4,4'-difluoro-6'-hydroxy-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001208]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 1049** (1.08 g, 3.65 mmol), **Intermediate 346** (1.60 g, 3.32 mmol), $K_3PO_4$ (1.92 g, 2.73 mmol) and XPhosPdG2 (0.24 g, 0.30 mmol) in 1,4-dioxane (72 mL) at 110 °C for 3 h. Purified by flash chromatography (80 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (1.71 g). LCMS (Method 15): 2.42 min, 516.2 $[M-H]^-$.

**Intermediate 1051:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-ethyl-4,4'-difluoro-5-(trifluoromethyl)-6'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate

**[001209]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 1050** (1.71 g, 3.65 mmol), phenyl triflimide (1.49 g, 4.17 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (1.63 g, 5.01 mmol) in DCM (13 mL) at RT for 2 h. Purified by flash chromatography (80 g silica gel, eluting 0–30% EtOAc in petroleum ether) to provide the title compound (2.60 g). LCMS (Method 15): 2.65 min, 648.2 $[M-H]^-$.

**Intermediate 1052:** Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-ethyl-4,4'-difluoro-6'-(hex-5-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001210]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 1051** (0.50 g, 0.69 mmol), 5-hexenylboronic acid (0.13 g, 1.04 mmol, CAS 1072952-16-9), $K_2CO_3$ (0.29 g, 2.08 mmol), palladium acetate (15 mg, 69 μmol) and RuPhos (48 mg, 0.10 mmol) in toluene (8.5 mL) and water (0.9 mL) at 95 °C for 1 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% EtOAc in petroleum ether) to provide the title compound (0.40 g). LCMS (Method 15): 2.87 min, 582.3 $[M-H]^-$.

**Intermediate 1053:** Ethyl (*S*)-3-amino-3-(2'-ethyl-4,4'-difluoro-6'-(hex-5-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001211]** A suspension of **Intermediate 1052** (1.35 g, 2.08 mmol) in 4 M HCl in 1,4-dioxane (5.2 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (1.39 g). LCMS (Method 15): 2.74 min, 484.2 $[M+H]^+$.

**Intermediate 1054:** Ethyl (*S*)-3-(2'-ethyl-4,4'-difluoro-6'-(hex-5-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[001212]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 1053** (1.39 g, 2.09 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.43 g, 3.34 mmol, CAS 413622-10-3), DIPEA (1.09 mL, 6.23 mmol), HOBt (0.31 g, 2.29 mmol) and EDCI (0.49 g, 3.13 mmol) in MeCN (19 mL) at RT for 16 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (1.0 g). LCMS (Method 15): 2.70 min, 582.3 $[M+H]^+$.

**Intermediate 1055:** Ethyl (*S*)-3-(2'-ethyl-4,4'-difluoro-6'-(hex-5-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[001213]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 1054** (0.40 g, 0.63 mmol), triethylamine (0.18 mL, 1.27 mmol) and methanesulfonyl chloride (73 µL, 0.95 mmol) in DCM (7 mL) at RT for 1 h, to provide the title compound (0.44 g). LCMS (Method 15): 2.74 min, 660.2 $[M+H]^+$.

**Intermediate 1056:** Ethyl (*S*)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(2'-ethyl-4,4'-difluoro-6'-(hex-5-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001214]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 1055** (0.44 g, 0.61 mmol), **Intermediate 258** (0.16 g, 0.68 mmol) and $K_2CO_3$ (0.25 g, 1.84 mmol) in MeCN (9 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.18 g). LCMS (Method 21): 6.27 min, 798.3 $[M+H]^+$.

**Intermediate 1057:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-ethyl-$1^4$,$2^4$-difluoro-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001215]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1056** (0.18 g, 0.21 mmol) in DCE (0.11 L) and Grubbs II (18 mg, 21 µmol) at 50 °C for 3 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.15 g). LCMS (Method 21): 6.02 min, 770.3 $[M+H]^+$.

**Intermediate 1058:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-ethyl-$1^4$,$2^4$-difluoro-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001216]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1057** (0.15 g, 0.14 mmol) and 10% palladium on carbon (15 mg) in ethanol (8 mL) under a hydrogen atmosphere at RT for 4 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.12 g). LCMS (Method 21): 6.07 min, 772.3 $[M+H]^+$.

**Intermediate 1059:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001217]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 997** (0.49 g, 0.68 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.18 g, 0.75 mmol, CAS 109919-32-6) and $K_2CO_3$ (0.28 g, 2.05 mmol) in MeCN (8 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (0.24 g). LCMS (Method 27): 2.80 min, 795.3 $[M-H]^-$.

**Intermediate 1060:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$-trifluoro-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001218]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1059** (0.24 g, 0.29 mmol) in DCE (0.15 L) and Grubbs II (25 mg, 29 µmol) at 50 °C for 2 h. Purified by flash chromatography (25 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.19 g). LCMS (Method 27): 2.51 min, 767.2 $[M-H]^-$.

**Intermediate 1061:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$-trifluoro-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001219]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 1060** (0.19 g, 0.22 mmol), $Pd(PPh_3)_2Cl_2$ (14 mg, 20 µmol), copper(I) iodide (3.0 mg, 16 µmol), triethylamine (0.26 mL, 1.84 mmol) and *N,N*-dimethylpropargylamine (0.20 mL, 1.84 mmol, CAS 7223-38-3) in MeCN (2.5 mL) at 80 °C for 24 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) then catch and release chromatography (SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.10 g). LCMS (Method 15): 2.72 min, 770.3 $[M+H]^+$.

**Intermediate 1062:** Ethyl 2-((3*S*,6*S*)-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$-trifluoro-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001220]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1061** (78 mg, 0.10 mmol) and 10% palladium on carbon (11 mg) in ethanol (3 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (77 mg). LCMS (Method 15): 2.84 min, 776.3 $[M+H]^+$.

**Intermediate 1063:** *tert*-Butyl (1-(hydroxymethyl)cyclohexyl)(methyl)carbamate

**[001221]** CDI (0.91 g, 5.63 mmol) was added to a stirred solution of 1-[*tert*-butoxycarbonyl(methyl)amino]cyclohexanecarboxylic acid (0.48 g, 1.88 mmol, CAS 1435805-19-8) in THF (11 mL) and stirred at RT for 1 h. The solution was cooled to 0 °C then sodium borohydride (0.21 g, 5.63 mmol) in water (18 mL) was added dropwise and stirred at 0 °C for 1 h. The mixture was diluted with 2 M aqueous HCl until pH 7 then extracted with EtOAc. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g silica gel, eluting 0-50% diethyl ether in petroleum ether) to provide the title compound (0.28 g). LCMS (Method 15): 1.98 min, 244.1 $[M+H]^+$.

**Intermediate 1064:** *tert*-Butyl (1-formylcyclohexyl)(methyl)carbamate

**[001222]** Dess Martin Periodinane (0.32 g, 0.76 mmol) was added to a stirred solution of **Intermediate 1063** (0.17 g, 0.69 mmol) in DCM (6.9 mL) and stirred at RT for 30 min. The reaction was quenched with 2 M sodium hydroxide (1.4 mL) and stirred at RT for 15 min. The mixture was extracted with DCM. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (0.28 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 9.36 (s, 1H), 2.88 (s, 3H), 2.03 – 1.96 (m, 2H), 1.67 – 1.52 (m, 8H), 1.43 (s, 9H).

**Intermediate 1065:** Ethyl 2-((3S,6S)-6-(((1-((*tert*-butoxycarbonyl)(methyl)amino)cyclohexyl)methyl)amino)-$1^4$,$2^4$,$2^5$-trifluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001223]** Prepared in an analogous manner to **Intermediate 940** using **Intermediate 1064** (18 mg, 75 µmol), triethylamine (47 µL, 0.34 mmol) and **Intermediate 1004** (36 mg, 68 µmol) in DCM (1 mL) with 4 Å molecular sieves at RT for 3 h, then STAB (72 mg, 0.34 mmol) at RT for 16 h. Purified by catch and release chromatography (SCX, eluting MeOH followed

by 7 M ammonia in MeOH) to provide the title compound (32 mg). LCMS (Method 15): 3.00 min, 716.5 $[M+H]^+$.

**Intermediate 1066:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$,$2^5$-trifluoro-$1^6$-methyl-6-(((1-(methylamino)cyclohexyl)methyl)amino)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001224]** A solution of **Intermediate 1065** (68 mg, 96 µmol) in DCM (8 mL) and 4 M HCl in 1,4-dioxane (0.24 mL) was stirred at RT for 18 h. The mixture was concentrated under reduced pressure, basified with saturated aqueous $NaHCO_3$ and extracted with DCM. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (52 mg). LCMS (Method 27): 3.07 min, 616.4 $[M+H]^+$.

**Intermediate 1067:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$,$2^5$-trifluoro-$1^6$-methyl-6-(1-methyl-2-oxo-1,3-diazaspiro[4.5]decan-3-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001225]** To a stirred solution of **Intermediate 1066** (18 mg, 30 µmol) and triethylamine (12 µL, 89 µmol) in MeCN (2.2 mL) was added triphosgene (18 mg, 59 µmol) and the mixture was stirred at RT for 18 h. The mixture was diluted with water and extracted with DCM. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (15 mg). LCMS (Method 15): 2.84 min, 642.3 $[M+H]^+$.

**Intermediate 1068:** 5,7-Dimethylbenzo[*c*][1,2]oxaborol-1(3*H*)-ol

**[001226]** To a solution of 3,5-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (3.02 g, 8.71 mmol, CAS 2602478-73-7) in MeOH (0.17 L) was added sodium borohydride (0.40 g, 10.4 mmol) and the mixture was stirred at RT for 1 h. The mixture was diluted with water then concentrated under reduced pressure. The residue was taken up in EtOAc and water then the organic layer was concentrated under reduced pressure. The residue was dissolved in THF (0.10 L) and 2 M aqueous HCl (8.71 mL) and stirred at RT for 1 h. The mixture was filtered and filtrate concentrated under reduced pressure and purified by flash chromatography (40 g silica, eluting 0-100% DCM in petroleum ether) to provide the title compound (0.27 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 6.96 (d, 2H), 5.01 (s, 2H), 2.50 (s, 3H), 2.37 (s, 3H) – OH not observed.

**Intermediate 1069**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-4-fluoro-2'-(hydroxymethyl)-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[001227]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 1068** (0.27 g, 1.58 mmol), **Intermediate 376** (0.51 g, 1.32 mmol), $K_3PO_4$ (0.84 g, 3.97 mmol) and XPhosPdG2 (0.10 g, 0.13 mmol) in 1,4-dioxane (8 mL) and water (1 mL) at 150 °C for 20 h.

Purified by flash chromatography (25 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.41 g). LCMS (Method 15): 2.47 min, 508.2 $[M+Na]^+$.

**Intermediate 1070:** (*S*)-3-(2'-((Allyloxy)methyl)-5-cyclopropyl-4-fluoro-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoic acid

**[001228]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 1069** (1.19 g, 1.57 mmol), sodium hydride (0.19 g, 1.37 mmol) and allyl bromide (4.08 mL, 47.2 mmol) in THF (30 mL) at RT for 18 h, to provide the title compound (0.83 g). LCMS (Method 15): 1.76 min, 496.2 $[M-H]^-$.

**Intermediate 1071:** Ethyl (*S*)-3-(2'-((allyloxy)methyl)-5-cyclopropyl-4-fluoro-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-aminopropanoate hydrochloride

**[001229]** A suspension of **Intermediate 1070** (0.83 g, 1.49 mmol) in 4 M HCl in 1,4-dioxane (11.2 mL) and ethanol (20 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.88 g). LCMS (Method 15): 2.58 min, 426.2 $[M+H]^+$.

**Intermediate 1072:** Ethyl (*S*)-3-(2'-((allyloxy)methyl)-5-cyclopropyl-4-fluoro-4',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxyhex-5-enamido)propanoate

**[001230]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 1071** (0.88 g, 1.39 mmol), (2*R*)-2-hydroxyhex-5-enoic acid (0.54 g, 4.17 mmol, CAS 612825-60-2), DIPEA (0.73 mL, 4.18 mmol), HOBt (0.26 g, 1.53 mmol) and EDCI (0.76 g, 4.87 mmol) in MeCN (28 mL) at RT for 17 h. Purified by flash chromatography (40 g silica gel, eluting 0-40% EtOAc in DCM) to provide the title compound (0.41 g). LCMS (Method 15): 2.60 min, 536.3 $[M-H]^-$.

**Intermediate 1073:** Ethyl 2-((3*S*,6*R*)-$2^5$-cyclopropyl-$2^4$-fluoro-6-hydroxy-$1^4$,$1^6$-dimethyl-5-oxo-12-oxa-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-9-en-3-yl)acetate

**[001231]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1072** (0.56 g, 0.89 mmol) in DCE (0.52 L) and Grubbs II (38 mg, 44 µmol) at 50 °C for 2 h. Purified by flash chromatography (40 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (0.38 g). LCMS (Method 15): 2.43 min, 510.2 $[M+H]^+$.

**Intermediate 1074:** Ethyl 2-((3*S*,6*R*)-$2^5$-cyclopropyl-$2^4$-fluoro-6-hydroxy-$1^4$,$1^6$-dimethyl-5-oxo-12-oxa-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001232]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1073** (0.38 g, 0.63 mmol) and 10% palladium on carbon (0.13 g) in EtOAc (63 mL) under a hydrogen atmosphere at RT for 1 h, to provide the title compound (0.33 g). LCMS (Method 15): 2.42 min, 512.3 $[M+H]^+$.

**Intermediate 1075:** Ethyl 2-((3*S*,6*R*)-2$^5$-cyclopropyl-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-6-((methylsulfonyl)oxy)-5-oxo-12-oxa-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001233]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 1074** (0.33 g, 0.53 mmol), triethylamine (0.22 mL, 1.60 mmol) and methanesulfonyl chloride (62 µL, 0.80 mmol) in DCM (85 mL) at RT for 1.5 h, to provide the title compound (0.37 g). LCMS (Method 15): 2.54 min, 590.2 $[M+H]^+$.

**Intermediate 1076:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-6-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-12-oxa-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001234]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 1075** (0.37 g, 0.56 mmol), **Intermediate 324** (0.30 g, 1.11 mmol) and $K_2CO_3$ (0.23 g, 1.67 mmol) in MeCN (56 mL) at reflux for 18 h. Purified by dry flash chromatography (silica gel, eluting EtOAc then 5% (1% ammonia MeOH) in DCM) to provide the title compound (0.35 g). LCMS (Method 15): 2.87 min, 754.3 $[M+H]^+$.

**Intermediate 1077:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4,4'-difluoro-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate

**[001235]** Prepared in an analogous manner to **Intermediate 6** using **Intermediate 984** (1.37 g, 2.72 mmol), $K_2CO_3$ (0.56 g, 4.08 mmol) and 4-bromobut-1-ene (0.30 mL, 2.99 mmol) in MeCN (25 mL) at reflux for 24 h. Additional $K_2CO_3$ (0.56 g, 4.08 mmol) and 4-bromobut-1-ene (0.30 mL, 2.99 mmol) were added and refluxed for 24 h. Purified by flash chromatography (24 g silica gel, eluting 0-20% EtOAc in petroleum ether) to provide the title compound (1.512 g). LCMS (Method 22): 2.14 min, 556.2 $[M-H]^-$.

**Intermediate 1078:** Ethyl (*S*)-3-amino-3-(2'-(but-3-en-1-yloxy)-4,4'-difluoro-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001236]** A suspension of **Intermediate 1077** (1.12 g, 1.81 mmol) in 4 M HCl in 1,4-dioxane (9 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (1.06 g). LCMS (Method 27): 1.72 min, 458.1 $[M+H]^+$.

**Intermediate 1079:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4,4'-difluoro-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxy-5-methylhex-5-enamido)propanoate

**[001237]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 1078** (0.89 g, 1.81 mmol), **Intermediate 983** (0.34 g, 2.35 mmol), DIPEA (1.26 mL, 7.22 mmol), HOBt (0.27 g, 1.99 mmol) and EDCI (0.52 g, 2.71 mmol) in MeCN (18 mL) at RT for 18 h.

Purified by flash chromatography (25 g silica gel, eluting 20-50% EtOAc in petroleum ether) to provide the title compound (0.33 g). LCMS (Method 22): 1.62 min, 584.2 $[M+H]^+$.

**Intermediate 1080:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4,4'-difluoro-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-5-methyl-2-((methylsulfonyl)oxy)hex-5-enamido)propanoate

**[001238]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 1079** (0.33 g, 0.53 mmol), triethylamine (0.15 mL, 1.06 mmol) and methanesulfonyl chloride (61 µL, 0.79 mmol) in DCM (5 mL) at RT for 1 h, to provide the title compound (0.35 g). LCMS (Method 22): 2.09 min, 662.1 $[M+H]^+$.

**Intermediate 1081:** Ethyl (*S*)-3-(2'-(but-3-en-1-yloxy)-4,4'-difluoro-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-methylhex-5-enamido)propanoate

**[001239]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 1080** (0.35 g, 0.53 mmol), **Intermediate 258** (0.19 g, 0.79 mmol) and $K_2CO_3$ (0.22 g, 1.58 mmol) in MeCN (6 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, eluting 2-4% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.20 g). LCMS (Method 18): 1.76 min, 798.4 $[M-H]^-$.

**Intermediate 1082:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$2^6$,7-dimethyl-11-oxo-$1^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-6-en-13-yl)acetate

**[001240]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1081** (0.18 g, 0.23 mmol) in toluene (75 mL) and Grubbs II (19 mg, 23 µmol) at 50 °C for 8 h. Purified by flash chromatography (40 g silica gel, eluting 2-6% (0.5% ammonia MeOH) in DCM) to provide the title compound (85 mg). LCMS (Method 22): 2.13 min, 772.3 $[M+H]^+$.

**Intermediate 1083:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$2^6$,7-dimethyl-11-oxo-$1^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[001241]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1082** (80 mg, 0.10 mmol) and 10% palladium on carbon (11 mg) in ethanol (2 mL) under a hydrogen atmosphere at RT for 74 h, to provide the title compound (52 mg). LCMS (Method 22): 1.62 min, 774.3 $[M+H]^+$.

**Intermediate 1084:** Ethyl (3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4,4'-difluoro-2'-(hex-5-en-2-yloxy)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001242]** To a solution of **Intermediate 984** (1.10 g, 2.03 mmol), hex-5-en-2-ol (0.26 g, 2.44 mmol, CAS 626-94-8) and triphenyl phosphine (1.07 g, 4.06 mmol) in THF (20 mL) at 0 °C was added DIAD (0.80 mL, 4.06 mmol) dropwise then the mixture was stirred at RT for 18 h. Additional hex-5-en-2-ol (0.26 g, 2.44 mmol), triphenyl phosphine (1.07 g, 4.06 mmol) and DIAD (0.80 mL, 4.06 mmol) were added and stirred at RT for 24 h. The mixture was concentrated under reduced pressure then purified by flash chromatography (12 g silica gel, eluting 100% DCM) to provide the title compound (0.38 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.40 – 7.33 (m, 2H), 6.62 – 6.43 (m, 2H), 5.79 – 5.62 (m, 2H), 5.39 (s, 1H), 4.98 – 4.89 (m, 2H), 4.30 – 4.19 (m, 1H), 4.15 – 3.98 (m, 2H), 2.93 – 2.85 (m, 2H), 2.15 – 1.87 (m, 5H), 1.67 – 1.46 (m, 2H), 1.40 (s, 9H), 1.21 – 1.11 (m, 5H) – NH not observed

**Intermediate 1085:** Ethyl (3*S*)-3-amino-3-(4,4'-difluoro-2'-(hex-5-en-2-yloxy)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001243]** A suspension of **Intermediate 1084** (0.37 g, 0.63 mmol) in 4 M HCl in 1,4-dioxane (4 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.41 g). LCMS (Method 22): 2.10 min, 486.1 $[M+H]^+$.

**Intermediate 1086:** Ethyl (3*S*)-3-(4,4'-difluoro-2'-(hex-5-en-2-yloxy)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[001244]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 1085** (0.38 g, 0.73 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.22 g, 1.90 mmol, CAS 413622-10-3), DIPEA (1.02 mL, 5.82 mmol), HOBt (0.22 g, 1.60 mmol) and EDCI (0.42 g, 2.18 mmol) in MeCN (7 mL) at RT for 64 h. Purified by flash chromatography (40 g silica gel, eluting 10-55% EtOAc in petroleum ether) to provide the title compound (0.24 g). LCMS (Method 22): 2.06 min, 584.2 $[M+H]^+$.

**Intermediate 1087:** Ethyl (3*S*)-3-(4,4'-difluoro-2'-(hex-5-en-2-yloxy)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[001245]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 1086** (0.24 g, 0.41 mmol), triethylamine (0.12 mL, 0.82 mmol) and methanesulfonyl chloride (48 µL, 0.62 mmol) in DCM (4 mL) at RT for 2 h, to provide the title compound (0.27 g). LCMS (Method 22): 2.10 min, 660.1 $[M-H]^-$.

**Intermediate 1088:** Ethyl (3*S*)-3-(4,4'-difluoro-2'-(hex-5-en-2-yloxy)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[001246]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 1087** (0.27 g, 0.41 mmol), **Intermediate 258** (0.14 g, 0.62 mmol) and $K_2CO_3$ (0.17 g, 1.23 mmol) in MeCN (5 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, eluting 2-4% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.15 g). LCMS (Method 22): 2.22 min, 798.3 $[M-H]^-$.

**Intermediate 1089:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$2^6$,4-dimethyl-11-oxo-$1^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphan-7-en-13-yl)acetate

**[001247]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1088** (0.15 g, 0.19 mmol) in toluene (65 mL) and Grubbs II (16 mg, 19 µmol) at 50 °C for 2.5 h. Purified by flash chromatography (40 g silica gel, eluting 2-10% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.11 g). LCMS (Method 22): 2.12 min, 772.3 $[M+H]^+$.

**Intermediate 1090:** Ethyl 2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$2^6$,4-dimethyl-11-oxo-$1^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetate

**[001248]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1089** (0.11 g, 0.14 mmol) and 10% palladium on carbon (15 mg) in ethanol (2 mL) under a hydrogen atmosphere at RT for 76 h, to provide the title compound (0.10 g). LCMS (Method 22): 2.12 min, 774.3 $[M+H]^+$.

**Intermediate 1091:** 4-(2-(6-Methoxy-4-(trifluoromethyl)pyridin-3-yl)ethyl)morpholine

**[001249]** Prepared in an analogous manner to **Intermediate 944** using **Intermediate 255** (2.0 g, 8.09 mmol) in TFA (10 mL) at RT for 5 h. followed by morpholine (1.41 mL, 16.2 mmol), triethylamine (1.35 mL, 9.71 mmol) and 4 Å molecular sieves in DCM (27 mL) at RT for 1 h. then STAB (3.43 g, 16.2 mmol) at RT for 16 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% (1 M ammonia MeOH) in DCM) to provide the title compound (1.59 g). LCMS (Method 15): 1.80 min, 291.0 $[M+H]^+$.

**Intermediate 1092:** 5-(2-Morpholinoethyl)-4-(trifluoromethyl)pyridin-2(1*H*)-one

**[001250]** A solution of **Intermediate 1091** (1.59 g, 5.48 mmol) in 33% HBr in AcOH (18.9 mL, 0.11 mol) was stirred at 85 °C for 2 h. The mixture was cooled and concentrated under reduced pressure. The crude product was purified by catch and release chromatography (10 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (1.42 g). LCMS (Method 15): 1.03 min, 277.0 $[M+H]^+$.

**Intermediate 1093:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-morpholinoethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[001251]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 638** (0.46 g, 0.64 mmol), **Intermediate 1092** (0.19 g, 0.70 mmol) and $K_2CO_3$ (0.26 g, 1.91 mmol) in MeCN (8 mL) at reflux for 16 h. Purified by flash chromatography (25 g silica gel, 0-60% EtOAc in petroleum ether) to provide the title compound (0.17 g). LCMS (Method 22): 2.20 min, 826.3 $[M+H]^+$.

**Intermediate 1094:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-$1^6$-methyl-6-(5-(2-morpholinoethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001252]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1093** (0.17 g, 0.21 mmol) in DCE (69 mL) and Grubbs II (18 mg, 0.10 mmol) at 50 °C for 1 h. Purified by flash chromatography (40 g silica gel, eluting 0-60% EtOAc in petroleum ether) to provide the title compound (0.13 g). LCMS (Method 22): 2.13 min, 798.3 $[M+H]^+$.

**Intermediate 1095:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-$1^6$-methyl-6-(5-(2-morpholinoethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001253]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1094** (0.15 g, 0.19 mmol) and 10% palladium on carbon (20 mg) in ethanol (18 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (12 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (0.11 g). LCMS (Method 22): 2.14 min, 800.3 $[M+H]^+$.

**Intermediate 1096:** Ethyl (*S*)-3-((*S*)-2-(3-Chloro-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001254]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 508** (1.06 g, 1.72 mmol), 6-chloro-4-(trifluoromethyl)pyridazin-3-ol (0.37 g, 1.89 mmol, CAS 2733139-85-8) and $K_2CO_3$ (0.71 g, 5.15 mmol) in DMF (10 mL) at 80 °C for 2 h. Purified by flash chromatography (24 g silica gel, 0-40% EtOAc in petroleum ether) to provide the title compound (0.97 g). LCMS (Method 15): 2.89 min, 718.3 $[M-H]^-$.

**Intermediate 1097:** Ethyl 2-((3*S*,6*S*)-6-(3-chloro-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001255]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1096** (1.04 g, 1.45 mmol) in DCE (0.46 L) and Grubbs II (0.12 g, 0.15 mmol) at 50 °C for 1 h. Purified by flash chromatography (24 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.85 g). LCMS (Method 15): 2.81 min, 692.3 $[M+H]^+$.

**Intermediate 1098:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(3-((*E*)-2-ethoxyvinyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001256]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 1097** (0.25 g, 0.36 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (79 mg, 0.40 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (26 mg, 36 µmol) and $Na_2CO_3$ (77 mg, 0.72 mmol) in toluene (2.9 mL) and water (1.0 mL) at 85 °C for 3 h. Purified by flash chromatography (24 g silica gel, eluting 0-40% EtOAc in petroleum ether), to provide the title compound (0.17 g). LCMS (Method 15): 2.86 min, 728.3 $[M+H]^+$.

**Intermediate 1099:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-6-(6-oxo-3-(2-oxoethyl)-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001257]** A solution of **Intermediate 1098** (0.17 g, 0.23 mmol) in DCM (11 mL) and TFA (1.1 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.16 g). LCMS (Method 15): 2.66 min, 700.3 $[M+H]^+$.

**Intermediate 1100:** Ethyl 2-((3*S*,6*S*)-6-(3-(2-(azetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001258]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 1099** (0.14 g, 0.20 mmol), azetidine (16 µL, 0.24 mmol), triethylamine (0.11 mL, 0.80 mmol) in DCM (3 mL) and 4 Å molecular sieves at RT for 3 h, then STAB (85 mg, 0.40 mmol) at RT for 18 h. Purified by catch and release chromatography (1 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (96 mg). LCMS (Method 15): 2.88 min, 741.3 $[M+H]^+$.

**Intermediate 1101:** Ethyl 2-((3*S*,6*S*)-6-(3-(2-(azetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001259]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1100** (96 mg, 0.13 mmol) and 10% palladium on carbon (14 mg) in ethanol (3.2 mL) under a

hydrogen atmosphere at RT for 12 h, to provide the title compound (70 mg). LCMS (Method 15): 2.91 min, 743.3 $[M+H]^+$.

**Intermediate 1102:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001260]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 1099** (0.16 g, 0.23 mmol), 3-fluoroazetidine hydrochloride (30 mg, 0.27 mmol, CAS 617718-46-4), triethylamine (94 µL, 0.68 mmol) in DCM (4.4 mL) and 4 Å molecular sieves at RT for 1.5 h, then STAB (96 mg, 0.45 mmol) at RT for 18 h. Purified by catch and release chromatography (1 g SCX, eluting MeOH followed by 7 M ammonia in MeOH) to provide the title compound (86 mg). LCMS (Method 15): 2.76 min, 759.3 $[M+H]^+$.

**Intermediate 1103:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001261]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1102** (86 mg, 0.11 mmol) and 10% palladium on carbon (12 mg) in ethanol (3 mL) under a hydrogen atmosphere at RT for 12 h. Purified by flash chromatography (4 g silica gel, eluting 0-5% (0.1% ammonia MeOH) in DCM), to provide the title compound (58 mg). LCMS (Method 15): 2.75 min, 761.3 $[M+H]^+$.

**Intermediate 1104:** Ethyl (*S*)-3-((*S*)-2-(3-chloro-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)pent-4-enamido)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001262]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 638** (0.43 g, 0.67 mmol), 6-chloro-4-(trifluoromethyl)pyridazin-3-ol (0.15 g, 0.73 mmol, CAS 2733139-85-8) and $K_2CO_3$ (0.28 g, 2.0 mmol) in DMF (7 mL) at 80 °C for 2 h. Purified by flash chromatography (24 g silica gel, 0-40% EtOAc in petroleum ether) to provide the title compound (0.30 g). LCMS (Method 15): 2.86 min, 748.3 $[M+H]^+$.

**Intermediate 1105:** Ethyl 2-((3*S*,6*S*)-6-(3-chloro-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001263]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1104** (0.30 g, 0.40 mmol) in DCE (0.13 L) and Grubbs II (34 mg, 40 µmol) at 45 °C for 1.5 h. Purified by flash chromatography (24 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.20 g). LCMS (Method 15): 2.77 min, 720.2 $[M+H]^+$.

**Intermediate 1106:** Ethyl 2-((3*S*,6*S*)-6-(3-((*E*)-2-ethoxyvinyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001264]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 1105** (0.20 g, 0.27 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (59 mg, 0.30 mmol, CAS 1201905-61-4), Pd(dppf)$Cl_2$ (20 mg, 27 μmol) and $Na_2CO_3$ (58 mg, 0.54 mmol) in toluene (2.3 mL) and water (0.8 mL) at 90 °C for 3 h. Purified by flash chromatography (24 g silica gel, eluting 0-40% EtOAc in petroleum ether), to provide the title compound (0.19 g). LCMS (Method 15): 2.84 min, 756.3 $[M+H]^+$.

**Intermediate 1107:** Ethyl 2-((3*S*,6*S*)-6-(3-(2-(azetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001265]** A solution of **Intermediate 1106** (0.19 g, 0.25 mmol) in DCM (5.5 mL) and TFA (0.38 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure then dissolved in DCM (5.5 mL). Azetidine (20 μL, 0.30 mmol), triethylamine (0.10 mL, 0.74 mmol) and 4 Å molecular sieves were added and stirred at RT for 1 h. STAB (0.10 g, 0.49 mmol) was added and stirred at RT for 3 h. The mixture was filtered and filtrate concentrated under reduced pressure and purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (78 mg). LCMS (Method 15): 2.85 min, 769.3 $[M+H]^+$.

**Intermediate 1108:** Ethyl 2-((3*S*,6*S*)-6-(3-(2-(azetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001266]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1107** (25 mg, 33 μmol) and 10% palladium on carbon (3.5 mg) in ethanol (2 mL) under a hydrogen atmosphere at RT for 4 h. Purified by flash chromatography (12 g silica gel, eluting 0-45% EtOAc in petroleum ether), to provide the title compound (10 mg). LCMS (Method 15): 2.85 min, 771.4 $[M+H]^+$.

**Intermediate 1109:** Ethyl (*S*)-3-((*S*)-2-(3-chloro-5-methyl-6-oxopyridazin-1(6*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001267]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 508** (0.46 g, 0.74 mmol), 3-chloro-5-methyl-1*H*-pyridazin-6-one (0.13 g, 0.89 mmol, CAS 1834-27-1) and $K_2CO_3$ (0.31 g, 2.23 mmol) in DMF (7 mL) at 80 °C for 18 h. Purified by flash

chromatography (25 g silica gel, 0-100% EtOAc in petroleum ether) to provide the title compound (0.45 g). LCMS (Method 15): 2.85 min, 666.3 $[M+H]^+$.

**Intermediate 1110:** Ethyl 2-((3*S*,6*S*)-6-(3-chloro-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001268]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1109** (0.45 g, 0.61 mmol) in DCE (0.20 L) and Grubbs II (52 mg, 61 µmol) at 50 °C for 1 h. Purified by flash chromatography (24 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.24 g). LCMS (Method 15): 2.78 min, 638.3 $[M+H]^+$.

**Intermediate 1111:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(3-((*E*)-2-ethoxyvinyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001269]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 1110** (0.24 g, 0.38 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (89 mg, 0.45 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (26 mg, 38 µmol) and $K_3PO_4$ (0.20 g, 0.94 mmol) in ethanol (5.6 mL) and water (0.6 mL) at 70 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-30% EtOAc in petroleum ether), to provide the title compound (0.18 g). LCMS (Method 15): 2.79 min, 674.3 $[M+H]^+$.

**Intermediate 1112:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-6-(5-methyl-6-oxo-3-((4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)methyl)pyridazin-1(6*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001270]** A solution of **Intermediate 1111** (0.17 g, 0.26 mmol) in DCM (13 mL) and TFA (1.3 mL) was stirred at RT for 1 h. The mixture was concentrated under reduced pressure to provide the title compound (0.29 g). LCMS (Method 15): 2.86 min, 746.4 $[M+H]^+$ - unexpected product due to pinacol not being removed in previous step.

**Intermediate 1113:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-6-(5-methyl-6-oxo-3-((4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)methyl)pyridazin-1(6*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001271]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1112** (0.16 g, 0.22 mmol) and 10% palladium on carbon (23 mg) in ethanol (7 mL) under a hydrogen atmosphere at RT for 6 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% (0.1% ammonia MeOH) in DCM), to provide the title compound (0.14 g). LCMS (Method 15): 2.88 min, 748.4 $[M+H]^+$.

**Intermediate 1114:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-6-(5-methyl-6-oxo-3-(2-oxoethyl)pyridazin-1(6*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001272]** A solution of **Intermediate 1113** (0.17 g, 0.20 mmol) in 4 M HCl in 1,4-dioxane (6.1 mL) and 2 M aqueous HCl (6.1 mL) was stirred at 60 °C for 3 h. Additional 2 M aqueous HCl (6.1 mL) was added and stirred at 60 °C for 3 h. The mixture diluted with DCM and the organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the title compound (0.14 g). LCMS (Method 15): 1.77 min, 648.3 $[M+H]^+$.

**Intermediate 1115:** Ethyl 2-((3*S*,6*S*)-6-(3-(2-(azetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001273]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 1114** (89 mg, 0.14 mmol), azetidine (12 µL, 0.17 mmol), triethylamine (80 µL, 0.57 mmol) in DCM (2 mL) and 4 Å molecular sieves at RT for 1 h, then STAB (61 mg, 0.29 mmol) at RT for 16 h. Purified by catch and release chromatography (2 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (36 mg). LCMS (Method 15): 3.19 min, 689.4 $[M+H]^+$.

**Intermediate 1116:** Ethyl 2-((3*S*,6*S*)-6-(3-(3-(dimethylamino)prop-1-yn-1-yl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001274]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 1105** (0.13 g, 0.19 mmol), $Pd(PPh_3)_2Cl_2$ (9 mg, 13 µmol), copper(I) iodide (2.5 mg, 13 µmol), triethylamine (0.18 mL, 1.29 mmol) and *N,N*-dimethylpropargylamine (0.14 mL, 1.29 mmol, CAS 7223-38-3) in MeCN (1.7 mL) at 75 °C for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.13 g). LCMS (Method 15): 2.76 min, 767.2 $[M+H]^+$.

**Intermediate 1117:** Ethyl 2-((3*S*,6*S*)-6-(3-(3-(dimethylamino)propyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001275]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1116** (0.13 g, 0.14 mmol) and 10% palladium on carbon (15 mg) in ethanol (15 mL) under a hydrogen atmosphere at RT for 16 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (67 mg). LCMS (Method 15): 2.78 min, 773.3 $[M+H]^+$.

**Intermediate 1118:** Ethyl (*S*)-3-((*S*)-2-(3-chloro-5-methyl-6-oxopyridazin-1(6*H*)-yl)pent-4-enamido)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001276]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 638** (1.43 g, 2.22 mmol), 3-chloro-5-methyl-1*H*-pyridazin-6-one (0.38 g, 2.66 mmol, CAS 1834-27-1) and $K_2CO_3$ (0.92 g, 6.64 mmol) in DMF (22 mL) at 80 °C for 2 h. Purified by flash chromatography (24 g silica gel, 0-50% EtOAc in petroleum ether) to provide the title compound (1.25 g). LCMS (Method 15): 2.80 min, 694.2 $[M+H]^+$.

**Intermediate 1119:** Ethyl 2-((3*S*,6*S*)-6-(3-chloro-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001277]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1118** (1.25 g, 1.80 mmol) in DCE (0.50 L) and Grubbs II (0.15 g, 0.18 mmol) at 50 °C for 1 h. Purified by flash chromatography (25 g silica gel, eluting 0-50% EtOAc in petroleum ether) to provide the title compound (0.98 g). LCMS (Method 15): 2.71 min, 666.2 $[M+H]^+$.

**Intermediate 1120:** Ethyl 2-((3*S*,6*S*)-6-(3-((*E*)-2-ethoxyvinyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001278]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 1119** (0.78 g, 1.17 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (0.26 g, 1.29 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (82 mg, 0.12 mmol) and $K_3PO_4$ (0.62 g, 2.94 mmol) in ethanol (18 mL) and water (1.8 mL) at 70 °C for 1.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-50% EtOAc in petroleum ether), to provide the title compound (0.45 g). LCMS (Method 15): 2.76 min, 702.2 $[M+H]^+$.

**Intermediate 1121:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001279]** Prepared in an analogous manner to **Intermediate 1107** using **Intermediate 1120** (0.15 g, 0.21 mmol), in DCM (2.7 mL) and TFA (0.33 mL) at RT for 1 h. Then 3-fluoroazetidine hydrochloride (29 mg, 0.26 mmol, CAS 617718-46-4), triethylamine (0.10 mL, 0.74 mmol) in DCM (9 mL) with 4 Å molecular sieves at RT for 15 min, followed by STAB (91 mg, 0.43 mmol) at RT for 2 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (86 mg). LCMS (Method 15): 2.63 min, 733.3 $[M+H]^+$.

**Intermediate 1122:** Ethyl 2-((3*S*,6*S*)-1$^4$,2$^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001280]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1121** (86 mg, 0.12 mmol) and 10% palladium on carbon (12 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 9 h, to provide the title compound (80 mg). LCMS (Method 15): 2.63 min, 735.3 $[M+H]^+$.

**Intermediate 1123:** Ethyl 2-((3*S*,6*S*)-1$^4$,2$^4$-difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001281]** Prepared in an analogous manner to **Intermediate 1107** using **Intermediate 1120** (0.16 g, 0.23 mmol), in DCM (2.9 mL) and TFA (0.35 mL) at RT for 2 h. Then 3-methoxyazetidine hydrochloride (34 mg, 0.27 mmol, CAS 148644-09-1), triethylamine (95 µL, 0.68 mmol) in DCM (10 mL) with 4 Å molecular sieves at RT for 15 min, followed by STAB (97 mg, 0.46 mmol) at RT for 2 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (91 mg). LCMS (Method 15): 2.61 min, 745.3 $[M+H]^+$.

**Intermediate 1124:** Ethyl 2-((3*S*,6*S*)-1$^4$,2$^4$-difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001282]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1123** (91 mg, 0.12 mmol) and 10% palladium on carbon (13 mg) in ethanol (11 mL) under a hydrogen atmosphere at RT for 9 h, to provide the title compound (99 mg). LCMS (Method 15): 2.63 min, 747.4 $[M+H]^+$.

**Intermediate 1125:** Ethyl 2-((3*S*,6*S*)-6-(3-(2-(azetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001283]** Prepared in an analogous manner to **Intermediate 1107** using **Intermediate 1120** (0.14 g, 0.20 mmol), in DCM (2.6 mL) and TFA (0.31 mL) at RT for 2 h. Then azetidine (16 µL, 0.24 mmol), triethylamine (85 µL, 0.61 mmol) in DCM (9 mL) with 4 Å molecular sieves at RT for 15 min, followed by STAB (86 mg, 0.41 mmol) at RT for 16 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (92 mg). LCMS (Method 15): 2.76 min, 715.4 $[M+H]^+$.

**Intermediate 1126:** Ethyl 2-((3*S*,6*S*)-6-(3-(2-(azetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001284]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1125** (92 mg, 0.13 mmol) and 10% palladium on carbon (14 mg) in ethanol (11 mL) under a hydrogen atmosphere at RT for 14 h, to provide the title compound (68 mg). LCMS (Method 15): 2.80 min, 717.3 $[M+H]^+$.

**Intermediate 1127:** Ethyl 2-((3*S*,6*S*)-6-(3-(3-(dimethylamino)prop-1-yn-1-yl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001285]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 1119** (0.20 g, 0.30 mmol), $Pd(PPh_3)_2Cl_2$ (15 mg, 21 µmol), copper(I) iodide (4 mg, 21 µmol), triethylamine (0.29 mL, 2.10 mmol) and *N,N*-dimethylpropargylamine (0.23 mL, 2.10 mmol, CAS 7223-38-3) in MeCN (1.7 mL) at 75 °C for 24 h. Additional $Pd(PPh_3)_2Cl_2$ (15 mg, 21 µmol), triethylamine (0.29 mL, 2.10 mmol) and *N,N*-dimethylpropargylamine (0.23 mL, 2.10 mmol) were added and heated at 75 °C for 24 h. Purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.14 g). LCMS (Method 15): 2.66 min, 713.3 $[M+H]^+$.

**Intermediate 1128:** Ethyl 2-((3*S*,6*S*)-6-(3-(3-(dimethylamino)propyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001286]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1127** (0.14 g, 0.20 mmol) and 10% palladium on carbon (21 mg) in ethanol (17 mL) under a hydrogen atmosphere at RT for 14 h, to provide the title compound (0.10 g). LCMS (Method 15): 2.66 min, 719.3 $[M+H]^+$.

**Intermediate 1129:** 6-Hydroxy-2-(4-methoxybenzyl)-5-(trifluoromethyl)pyridazin-3(2*H*)-one

**[001287]** To a solution of 3-(trifluoromethyl)furan-2,5-dione (10 g, 60.2 mmol, CAS 700-27-6) in AcOH (0.21 L) was added (4-methoxyphenyl)methylhydrazine hydrochloride (11.4 g, 60.2 mmol) then the mixture was stirred at 100 °C for 6 h. The mixture was cooled and diluted with water. The solid was filtered, washing with water, then triturated in 1:1 diethyl ether / petroleum ether, to provide the title compound (6.16 g). LCMS (Method 7): 1.56 min, 301.0 $[M+H]^+$.

**Intermediate 1130:** 1-(4-Methoxybenzyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridazin-3-yl trifluoromethanesulfonate

**[001288]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 1129** (3.0 g, 9.99 mmol), phenyl triflimide (3.57 g, 9.99 mmol, CAS 37595-74-7) and triethylamine (2.09 mL, 15.0 mmol) in MeCN (13 mL) at RT for 5 h. Purified by flash chromatography (80 g silica gel, eluting 0–50% EtOAc in petroleum ether) to provide the title compound (3.10 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.38 (d, 2H), 7.31 (s, 1H), 6.88 (d, 2H), 5.18 (s, 2H), 3.80 (s, 3H).

**Intermediate 1131:** 6-(3-(Dimethylamino)prop-1-yn-1-yl)-2-(4-methoxybenzyl)-5-(trifluoromethyl)pyridazin-3(2*H*)-one

**[001289]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 1130** (0.51 g, 1.19 mmol), $Pd(PPh_3)_2Cl_2$ (58 mg, 83 μmol), copper(I) iodide (16 mg, 83 μmol), triethylamine (1.16 mL, 8.31 mmol) and *N,N*-dimethylpropargylamine (0.90 mL, 8.31 mmol, CAS 7223-38-3) in MeCN (32 mL) at 80 °C for 18 h. Purified by flash chromatography (12 g silica gel, eluting 50–100% EtOAc in petroleum ether) then catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.34 g). LCMS (Method 15): 1.99 min, 366.1 $[M+H]^+$.

**Intermediate 1132:** 6-(3-(Dimethylamino)propyl)-2-(4-methoxybenzyl)-5-(trifluoromethyl)pyridazin-3(2*H*)-one

**[001290]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1131** (0.34 g, 0.93 mmol) and 10% palladium on carbon (99 mg) in ethanol (22 mL) under a hydrogen atmosphere at RT for 14 h. Purified by flash chromatography (12 g silica gel, eluting 5–10% MeOH in DCM) to provide the title compound (0.31 g). LCMS (Method 15): 2.03 min, 370.1 $[M+H]^+$.

**Intermediate 1133:** 6-(3-(Dimethylamino)propyl)-5-(trifluoromethyl)pyridazin-3(2*H*)-one

**[001291]** To a solution of **Intermediate 1132** (0.31 g, 0.84 mmol) in MeCN (4.7 mL) was added CAN (1.84 g, 3.36 mmol) in water (1.6 mL) dropwise. The solution was stirred at RT for 30 min. The mixture was concentrated under reduced pressure and purified by catch and release chromatography (5 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (0.20 g). LCMS (Method 15): 1.16 min, 250.0 $[M+H]^+$.

**Intermediate 1134:** Ethyl (*S*)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(3-(3-(dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)pent-4-enamido)propanoate

**[001292]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 638** (0.40 g, 0.61 mmol), **Intermediate 1133** (0.15 g, 0.61 mmol) and $K_2CO_3$ (0.25 g, 1.84 mmol) in DMF (10 mL) at 80 °C for 16 h. Purified by flash chromatography (40 g silica gel, 0-10%

MeOH in DCM) to provide the title compound (75 mg). LCMS (Method 15): 2.95 min, 799.4 $[M+H]^+$.

**Intermediate 1135:** Ethyl 2-((3*S*,6*S*)-6-(3-(3-(dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001293]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1134** (75 mg, 69 µmol) in DCE (50 mL) and Grubbs II (5.8 mg, 7 µmol) at 50 °C for 5 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (45 mg). LCMS (Method 15): 2.88 min, 771.4 $[M+H]^+$.

**Intermediate 1136:** Ethyl 2-((3*S*,6*S*)-6-(3-(3-(dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001294]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1135** (45 mg, 33 µmol) and 10% palladium on carbon (3.5 mg) in ethanol (1.4 mL) under a hydrogen atmosphere at RT for 6 h. Purified by flash chromatography (4 g silica gel, eluting 0–10% MeOH in DCM) to provide the title compound (31 mg). LCMS (Method 15): 2.91 min, 773.4 $[M+H]^+$.

**Intermediate 1137:** 6-Chloro-5-(trifluoromethyl)pyridazin-3(2*H*)-one

**[001295]** To a solution of 3,6-dichloro-4-(trifluoromethyl)pyridazine (0.85 g, 3.92 mmol, CAS 1057672-68-0) in 1,4-dioxane (5 mL) and water (4.5 mL) was added sodium hydroxide (0.17 g, 4.31 mmol) and the mixture was stirred at 40 °C for 1 h. The mixture was acidified with 2 M aqueous HCl and extracted into EtOAc. The organic layer was washed with water, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (40 g silica gel, eluting 0–4% MeOH in DCM) to provide the title compound (0.61 g). $^1$H NMR (400 MHz; DMSO-$d_6$) δ: 13.83 (br s, 1H), 8.06 (s, 1H).

**Intermediate 1138:** Ethyl (*S*)-3-((*S*)-2-(3-chloro-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)pent-4-enamido)-3-(4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

**[001296]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 638** (0.54 g, 0.69 mmol), **Intermediate 1137** (0.16 g, 0.83 mmol) and $K_2CO_3$ (0.29 g, 2.07 mmol) in DMF (7 mL) at 80 °C for 2 h. Purified by flash chromatography (40 g silica gel, 0-50% EtOAc in petroleum ether) to provide the title compound (0.34 g). LCMS (Method 15): 2.92 min, 748.3 $[M+H]^+$.

**Intermediate 1139:** Ethyl 2-((3*S*,6*S*)-6-(3-chloro-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001297]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1138** (0.34 g, 0.44 mmol) in DCE (0.21 L) and Grubbs II (37 mg, 44 µmol) at 50 °C for 2 h. Purified by flash chromatography (25 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.24 g). LCMS (Method 15): 2.82 min, 720.1 $[M+H]^+$.

**Intermediate 1140:** Ethyl 2-((3*S*,6*S*)-6-(3-((*E*)-2-ethoxyvinyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001298]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 1139** (0.24 g, 0.30 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (65 mg, 0.33 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (22 mg, 30 µmol) and $Na_2CO_3$ (64 mg, 0.60 mmol) in toluene (4.5 mL) and water (1.5 mL) at 90 °C for 3 h. Extra *trans*-2-ethoxyvinylboronic acid pinacol ester (65 mg, 0.33 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (22 mg, 30 µmol) and $Na_2CO_3$ (64 mg, 0.60 mmol) were added and heated at 90 °C for 24 h. Purified by flash chromatography (25 g silica gel, eluting 0-30% EtOAc in petroleum ether). Conditions repeated with *trans*-2-ethoxyvinylboronic acid pinacol ester (65 mg, 0.33 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (22 mg, 30 µmol) and $Na_2CO_3$ (64 mg, 0.60 mmol) in toluene (4.5 mL) and water (1.5 mL) at 90 °C for 18 h, and purified by flash chromatography (25 g silica gel, eluting 0-25% EtOAc in petroleum ether), to provide the title compound (93 mg). LCMS (Method 15): 2.89 min, 756.3 $[M+H]^+$.

**Intermediate 1141:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001299]** Prepared in an analogous manner to **Intermediate 1107** using **Intermediate 1140** (50 mg, 66 µmol), in DCM (1.5 mL) and TFA (0.10 mL) at RT for 1 h. Then 3-fluoroazetidine hydrochloride (8.9 mg, 79 µmol, CAS 617718-46-4), triethylamine (28 µL, 0.20 mmol) in DCM (1.5 mL) with 4 Å molecular sieves at RT for 1 h, followed by STAB (28 mg, 0.13 mmol) at RT for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (37 mg). LCMS (Method 15): 2.76 min, 787.3 $[M+H]^+$.

**Intermediate 1142:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001300]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1141** (37 mg, 41 μmol) and 10% palladium on carbon (4.4 mg) in ethanol (0.8 mL) under a hydrogen atmosphere at RT for 6 h. Purified by flash chromatography (4 g silica gel, eluting 0–10% MeOH in DCM) to provide the title compound (27 mg). LCMS (Method 15): 2.78 min, 789.3 $[M+H]^+$.

**Intermediate 1143:** Ethyl (*S*)-3-((*S*)-2-(3-chloro-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)hex-5-enamido)-3-(4,4'-difluoro-2'-(hex-4-en-1-yl)-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

**[001301]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 953** (0.37 g, 0.61 mmol), **Intermediate 1137** (0.11 g, 0.56 mmol) and $K_2CO_3$ (0.19 g, 1.40 mmol) in DMF (4 mL) at 80 °C for 3 h. Purified by flash chromatography (25 g silica gel, 0-40% EtOAc in petroleum ether) to provide the title compound (0.24 g). LCMS (Method 15): 2.95 min, 708.2 $[M+H]^+$.

**Intermediate 1144:** Ethyl 2-((3*S*,6*S*)-6-(3-chloro-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-9-en-3-yl)acetate

**[001302]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1143** (0.24 g, 0.34 mmol) in DCE (0.11 L) and Grubbs II (29 mg, 34 μmol) at 50 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.19 g). LCMS (Method 15): 2.80 min, 666.2 $[M+H]^+$.

**Intermediate 1145:** Ethyl 2-((3*S*,6*S*)-6-(3-(3-(dimethylamino)prop-1-yn-1-yl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-9-en-3-yl)acetate

**[001303]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 1144** (0.15 g, 0.23 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg, 16 μmol), copper(I) iodide (3 mg, 16 μmol), triethylamine (0.22 mL, 1.59 mmol) and *N,N*-dimethylpropargylamine (0.17 mL, 1.59 mmol, CAS 7223-38-3) in MeCN (4 mL) at 80 °C for 16 h. Purified by flash chromatography (12 g silica gel, eluting 0–5% (0.5% ammonia MeOH) in DCM) then catch and release chromatography (2 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (76 mg). LCMS (Method 15): 2.74 min, 713.3 $[M+H]^+$.

**Intermediate 1146:** Ethyl 2-((3*S*,6*S*)-6-(3-(3-(dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001304]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1145** (76 mg, 0.11 mmol) and 10% palladium on carbon (22 mg) in ethanol (3 mL) under a hydrogen

atmosphere at RT for 7 h. Purified by flash chromatography (4 g silica gel, eluting 0–10% (0.1% ammonia MeOH) in DCM) to provide the title compound (72 mg). LCMS (Method 15): 2.93 min, 719.3 $[M+H]^+$.

**Intermediate 1147:** Ethyl (*S*)-3-((*S*)-2-(3-chloro-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001305]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 508** (1.14 g, 1.85 mmol), **Intermediate 1137** (0.34 g, 0.92 mmol) and $K_2CO_3$ (0.59 g, 4.26 mmol) in DMF (13 mL) at 80 °C for 2 h. Purified by flash chromatography (24 g silica gel, 0-30% EtOAc in petroleum ether) to provide the title compound (0.62 g). LCMS (Method 15): 2.96 min, 720.3 $[M+H]^+$.

**Intermediate 1148:** Ethyl 2-((3*S*,6*S*)-6-(3-chloro-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001306]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1147** (0.62 g, 0.87 mmol) in DCE (0.28 L) and Grubbs II (74 mg, 87 µmol) at 50 °C for 2 h. Purified by flash chromatography (24 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.43 g). LCMS (Method 15): 2.82 min, 692.2 $[M+H]^+$.

**Intermediate 1149:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(3-(3-(dimethylamino)prop-1-yn-1-yl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001307]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 1148** (0.15 g, 0.22 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg, 15 µmol), copper(I) iodide (3 mg, 15 µmol), triethylamine (0.11 mL, 0.77 mmol) and *N,N*-dimethylpropargylamine (0.17 mL, 1.55 mmol, CAS 7223-38-3) in MeCN (4.5 mL) at 80 °C for 20 h. Purified by flash chromatography (12 g silica gel, eluting 0–5% (0.5% ammonia MeOH) in DCM) then catch and release chromatography (2 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (48 mg). LCMS (Method 15): 2.77 min, 739.3 $[M+H]^+$.

**Intermediate 1150:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(3-(3-(dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001308]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1149** (45 mg, 61 µmol) and 10% palladium on carbon (26 mg) in isobutanol (1.7 mL) under a hydrogen atmosphere at RT for 6 h. Purified by flash chromatography (4 g silica gel, eluting

0–10% (0.1% ammonia MeOH) in DCM) to provide the title compound (29 mg). LCMS (Method 15): 2.98 min, 745.4 $[M+H]^+$.

**Intermediate 1151:** Ethyl 2-((3*S*,6*S*)-6-(3-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-yn-1-yl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001309]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 1139** (0.50 g, 0.69 mmol), $Pd(PPh_3)_2Cl_2$ (49 mg, 69 µmol), copper(I) iodide (26 mg, 0.14 mmol), triethylamine (0.97 mL, 6.94 mmol) and *tert*-butyldimethyl-prop-2-ynoxy-silane (1.41 mL, 6.94 mmol, CAS 76782-82-6) in DMF (3.5 mL) at 110 °C for 5 h. Purified by flash chromatography (25 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.42 g). LCMS (Method 19): 6.64 min, 854.3 $[M+H]^+$.

**Intermediate 1152:** Ethyl 2-((3*S*,6*S*)-6-(3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001310]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1151** (0.37 g, 0.44 mmol) and 10% palladium on carbon (46 mg) in ethanol (15 mL) under a hydrogen atmosphere at RT for 7 h. Purified by flash chromatography (12 g silica gel, eluting 0–100% EtOAc in petroleum ether) to provide the title compound (0.17 g). LCMS (Method 21): 6.85 min, 860.3 $[M+H]^+$.

**Intermediate 1153:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(3-(3-hydroxypropyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001311]** Prepared in an analogous manner to **Intermediate 757** using **Intermediate 1152** (0.22 g, 0.26 mmol) and TBAF (1 M in THF, 0.76 mL, 0.76 mmol) in THF (2.3 mL) at RT for 3 h. Purified by flash chromatography (25 g silica gel, eluting 0-100% EtOAc in petroleum ether) to provide the title compound (89 mg). LCMS (Method 15): 2.61 min, 746.2 $[M+H]^+$.

**Intermediate 1154:** Ethyl 2-((3*S*,6*S*)-6-(3-(3-(azetidin-1-yl)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001312]** Prepared in an analogous manner to **Intermediate 758** using **Intermediate 1153** (0.16 g, 0.22 mmol), triphenylphosphine (0.11 g, 0.44 mmol), carbon tetrabromide (0.14 g, 0.44 mmol) in DCM (3.3 mL) at RT for 2 h, followed by azetidine (0.15 mL, 2.19 mmol) and $K_2CO_3$ (59 mg, 0.43 mmol) in MeCN (3.3 mL) at RT for 16 h. Purified by flash chromatography

(25 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (87 mg). LCMS (Method 15): 2.95 min, 785.3 $[M+H]^+$.

**Intermediate 1155:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(3-((*E*)-2-ethoxyvinyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001313]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 1148** (0.14 g, 0.20 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (43 mg, 0.22 mmol, CAS 1201905-61-4), Pd(dppf)$Cl_2$ (15 mg, 20 µmol) and $Na_2CO_3$ (42 mg, 0.39 mmol) in toluene (1.2 mL) and water (0.3 mL) at 125 °C for 8 h. Purified by flash chromatography (12 g silica gel, eluting 0-50% EtOAc in petroleum ether), to provide the title compound (75 mg). LCMS (Method 15): 2.89 min, 728.3 $[M+H]^+$.

**Intermediate 1156:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001314]** Prepared in an analogous manner to **Intermediate 1107** using **Intermediate 1155** (75 mg, 0.10 mmol), in DCM (2.5 mL) and TFA (0.16 mL) at RT for 2 h. Then 3-methoxyazetidine hydrochloride (15 mg, 0.12 mmol, CAS 148644-09-1), triethylamine (57 µL, 0.41 mmol) in DCM (4.5 mL) with 4 Å molecular sieves at RT for 15 min, followed by STAB (44 mg, 0.21 mmol) at RT for 2 h. Purified by catch and release chromatography (2 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (37 mg). LCMS (Method 15): 2.74 min, 771.3 $[M+H]^+$.

**Intermediate 1157:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001315]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1156** (37 mg, 48 µmol) and 10% palladium on carbon (10 mg) in ethanol (1.5 mL) under a hydrogen atmosphere at RT for 48 h. Purified by flash chromatography (4 g silica gel, eluting 0–10% (0.1% ammonia MeOH) in DCM) to provide the title compound (27 mg). LCMS (Method 15): 2.75 min, 773.4 $[M+H]^+$.

**Intermediate 1158:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001316]** Prepared in an analogous manner to **Intermediate 1107** using **Intermediate 1155** (78 mg, 0.11 mmol), in DCM (2.3 mL) and TFA (0.17 mL) at RT for 1 h. Then 3-

fluoroazetidine hydrochloride (14 mg, 0.13 mmol, CAS 617718-46-4), triethylamine (45 µL, 0.32 mmol) in DCM (2.3 mL) with 4 Å molecular sieves at RT for 1 h, followed by STAB (45 mg, 0.21 mmol) at RT for 18 h. Purified by catch and release chromatography (1 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (23 mg). LCMS (Method 15): 2.76 min, 759.2 $[M+H]^+$.

**Intermediate 1159:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001317]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1158** (25 mg, 33 µmol) and 10% palladium on carbon (7 mg) in ethanol (0.9 mL) under a hydrogen atmosphere at RT for 54 h. Purified by flash chromatography (4 g silica gel, eluting 0–10% (0.1% ammonia MeOH) in DCM) to provide the title compound (25 mg). LCMS (Method 15): 2.75 min, 761.3 $[M+H]^+$.

**Intermediate 1160:** Ethyl 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001318]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 720** (0.11 g, 0.15 mmol) and 10% palladium on carbon (16 mg) in ethanol (6 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (4 g silica gel, eluting 10% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.11 g). LCMS (Method 15): 2.67 min, 690.3 $[M+H]^+$.

**Intermediate 1161:** Ethyl 2-((3*S*,6*S*)-6-(3-(2-(dimethylamino)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001319]** Prepared in an analogous manner to **Intermediate 1107** using **Intermediate 714** (0.18 g, 0.24 mmol), in DCM (2.3 mL) and TFA (0.4 mL) at RT for 1 h. Then dimethylamine (2 M in THF, 0.14 mL, 0.28 mmol), triethylamine (98 µL, 0.71 mmol) in DCM (2.3 mL) with 4 Å molecular sieves at RT for 1 h, followed by STAB (0.20 g, 2.36 mmol) at RT for 72 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (81 mg). LCMS (Method 15): 2.82 min, 759.3 $[M+H]^+$.

**Intermediate 1162:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001320]** Prepared in an analogous manner to **Intermediate 137** using **Intermediate 1114** (0.14 g, 94 µmol), 3-fluoroazetidine hydrochloride (13 mg, 0.11 mmol, CAS 617718-46-4), triethylamine (52 µL, 0.37 mmol) in DCM (5 mL) and 4 Å molecular sieves at RT for 1 h, then STAB (40 mg, 0.19 mmol) at RT for 16 h. Purified by catch and release chromatography (2 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (35 mg). LCMS (Method 15): 2.73 min, 707.3 $[M+H]^+$.

**Intermediate 1163:** Ethyl 2-((3*S*,6*S*)-6-(3-chloro-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001321]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1144** (0.47 g, 0.55 mmol) and 10% palladium on carbon (59 mg) in EtOAc (24 mL) under a hydrogen atmosphere at RT for 3 h. Purified by flash chromatography (4 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.45 g). LCMS (Method 15): 2.83 min, 668.2 $[M+H]^+$.

**Intermediate 1164:** Ethyl 2-((3*S*,6*S*)-6-(3-((*E*)-2-ethoxyvinyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001322]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 1163** (0.40 g, 0.49 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (0.22 g, 1.06 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (70 mg, 96 µmol) and $Na_2CO_3$ (0.11 g, 0.97 mmol) in toluene (5.6 mL) and water (1.9 mL) at 90 °C for 24 h. Conditions repeated. Purified by flash chromatography (40 g silica gel, eluting 0-25% EtOAc in petroleum ether), to provide the title compound (0.15 g). LCMS (Method 15): 2.89 min, 704.2 $[M+H]^+$.

**Intermediate 1165:** Ethyl 2-((3*S*,6*S*)-$1^4$,$2^4$-difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001323]** Prepared in an analogous manner to **Intermediate 1107** using **Intermediate 1164** (0.12 g, 0.15 mmol), in DCM (3.3 mL) and TFA (0.23 mL) at RT for 1 h. Then 3-methoxyazetidine hydrochloride (22 mg, 0.18 mmol, CAS 148644-09-1), triethylamine (61 µL, 0.44 mmol) in DCM (3.3 mL) with 4 Å molecular sieves at RT for 1 h, followed by STAB (62 mg, 0.29 mmol) at RT for 18 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (76 mg). LCMS (Method 15): 2.72 min, 747.3 $[M+H]^+$.

**Intermediate 1166:** Ethyl (*S*)-3-((*S*)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)propanoate

**[001324]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 739** (1.21 g, 1.65 mmol), 5-bromo-4-(trifluoromethyl)pyridin-2-ol (0.60 g, 2.48 mmol, CAS 109919-32-6) and $K_2CO_3$ (0.69 g, 4.96 mmol) in MeCN (17 mL) at reflux for 18 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (0.70 g). LCMS (Method 15): 2.80 min, 767.2 $[M-H]^-$.

**Intermediate 1167:** Ethyl 2-((3*S*,6*S*)-6-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$1^6$,$2^4$-trifluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001325]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1166** (0.70 g, 0.79 mmol) in DCE (0.40 L) and Grubbs II (85 mg, 0.10 mmol) at 50 °C for 1 h. Purified by flash chromatography (24 g silica gel, eluting 0-25% EtOAc in petroleum ether) to provide the title compound (0.48 g). LCMS (Method 15): 2.79 min, 741.1 $[M+H]^+$.

**Intermediate 1168:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(5-((*E*)-2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$-trifluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001326]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 1167** (0.48 g, 0.63 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (0.13 g, 0.66 mmol, CAS 1201905-61-4), $Pd(dppf)Cl_2$ (92 mg, 0.13 mmol) and $Na_2CO_3$ (0.13 g, 1.25 mmol) in toluene (13 mL) and water (4 mL) at 85 °C for 4 h. Purified by flash chromatography (40 g silica gel, eluting 0-25% EtOAc in petroleum ether), to provide the title compound (0.31 g). LCMS (Method 15): 2.85 min, 731.2 $[M+H]^+$.

**Intermediate 1169:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-$1^4$,$1^6$,$2^4$-trifluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001327]** Prepared in an analogous manner to **Intermediate 1107** using **Intermediate 1168** (0.31 g, 0.32 mmol), in DCM (16 mL) and TFA (0.5 mL) at RT for 1 h. Then 3-methoxyazetidine hydrochloride (43 mg, 0.39 mmol, CAS 148644-09-1), triethylamine (0.14 mL, 0.97 mmol) in DCM (16 mL) with 4 Å molecular sieves at RT for 1 h, followed by STAB (0.14 g, 0.65 mmol) at RT for 20 h. Purified by catch and release chromatography (20 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (96 mg). LCMS (Method 15): 2.69 min, 774.3 $[M+H]^+$.

**Intermediate 1170:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-1$^4$,1$^6$,2$^4$-trifluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001328]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1169** (96 mg, 93 µmol) and 10% palladium on carbon (10 mg) in ethanol (10 mL) under a hydrogen atmosphere at RT for 5 h. Purified by flash chromatography (4 g silica gel, eluting EtOAc) to provide the title compound (0.11 g). LCMS (Method 15): 2.70 min, 776.3 $[M+H]^+$.

**Intermediate 1171:** Ethyl (*S*)-3-((*S*)-2-(3-chloro-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)pent-4-enamido)-3-(4,4',5-trifluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001329]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 829** (0.40 g, 0.67 mmol), **Intermediate 1137** (0.16 g, 0.80 mmol) and $K_2CO_3$ (0.28 g, 2.01 mmol) in MeCN (7 mL) at reflux for 3 h. Purified by flash chromatography (40 g silica gel, 0-40% EtOAc in petroleum ether) to provide the title compound (0.23 g). LCMS (Method 15): 2.85 min, 698.3 $[M+H]^+$.

**Intermediate 1172:** Ethyl 2-((3*S*,6*S*)-6-(3-chloro-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$,2$^5$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001330]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1171** (0.23 g, 0.33 mmol) in DCE (0.11 L) and Grubbs II (30 mg, 0.11 mmol) at 40 °C for 1.5 h. Purified by flash chromatography (12 g silica gel, eluting 0-40% EtOAc in petroleum ether) to provide the title compound (0.19 g). LCMS (Method 15): 2.73 min, 670.2 $[M+H]^+$.

**Intermediate 1173:** Ethyl 2-((3*S*,6*S*)-6-(3-(3-(dimethylamino)prop-1-yn-1-yl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$,2$^5$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001331]** Prepared in an analogous manner to **Intermediate 370** using **Intermediate 1172** (0.19 g, 0.26 mmol), $Pd(PPh_3)_2Cl_2$ (13 mg, 18 µmol), copper(I) iodide (3.5 mg, 18 µmol), triethylamine (0.26 mL, 1.83 mmol) and *N,N*-dimethylpropargylamine (0.20 mL, 1.83 mmol, CAS 7223-38-3) in MeCN (4.2 mL) at 80 °C for 16 h. Purified by flash chromatography (12 g silica gel, eluting 0–5% (0.5% ammonia MeOH) in DCM) then catch and release chromatography (2 g SCX, eluting MeOH followed by 3.5 M ammonia in MeOH) to provide the title compound (70 mg). LCMS (Method 15): 2.67 min, 717.2 $[M+H]^+$.

**Intermediate 1174:** Ethyl 2-((3*S*,6*S*)-6-(3-(3-(dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$,2$^5$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001332]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1173** (60 mg, 74 µmol) and 10% palladium on carbon (7.8 mg) in ethanol (5 mL) under a hydrogen atmosphere at RT for 11 h. Purified by flash chromatography (4 g silica gel, eluting 0-5% (0.1% ammonia MeOH) in DCM) to provide the title compound (30 mg). LCMS (Method 27): 2.33 min, 723.4 $[M+H]^+$.

**Intermediate 1175:** Potassium (6-methylhept-5-en-1-yl)trifluoroborate

**[001333]** A mixture of magnesium (0.75 g, 30.9 mmol) and iodine (0.55 g, 2.17 mmol) was heated at 30 °C under nitrogen. To this was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.53 g, 27.6 mmol, CAS 25015-63-8) in THF (100 mL) followed by dropwise addition of 7-bromo-2-methyl-hept-2-ene (4.3 g, 22.5 mmol, CAS 58335-23-2) in THF (10 mL) and the mixture stirred at RT for 2 h. The mixture was cooled to 0 °C and acidified using 2 M aqueous HCl. The mixture was extracted with EtOAc then the organics washed with brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (80 g silica gel, eluting 0-10% EtOAc in petroleum ether). The residue was dissolved in MeOH and added slowly to a solution of potassium hydrogenfluoride (3.0 g, 38.4 mmol, CAS 7789-29-9) in water (25 mL) then stirred at RT for 1 h. The liquid was decanted off and the solid triturated in warm acetone. The combined liquids were concentrated under reduced pressure. The residue was dissolved in 1:1 MeOH / water and concentrated under reduced pressure. The solid was dissolved in minimal hot acetone and precipitated by addition of petroleum ether, filtered washing with petroleum ether, to provide the title compound (2.3 g). $^1$H NMR (400 MHz; DMSO-$d_6$) δ: 5.23 – 4.85 (m, 1H), 1.87 (q, 2H), 1.63 (s, 3H), 1.54 (s, 3H), 1.25 – 1.04 (m, 4H), -0.04 – -0.14 (m, 2H).

**Intermediate 1176:** 3,4-Difluoro-6-methyl-2-(6-methylhept-5-en-1-yl)phenol

**[001334]** Prepared in an analogous manner to **Intermediate 3** using 2-bromo-3,4-difluoro-6-methyl-phenol (0.92 g, 4.14 mmol, CAS 1780882-44-1), **Intermediate 1175** (1.37 g, 6.06 mmol), $K_2CO_3$ (1.70 g, 2.97 mmol), RuPhosPdG3 (0.35 g, 0.42 mmol) and RuPhos (0.20 g, 0.43 mmol) in toluene (35 mL) and water (5 mL) at 95 °C for 20 h. Purified by flash chromatography (80 g silica gel, eluting 0-5% EtOAc in petroleum ether) to provide the title compound (0.76 g). LCMS (Method 23): 2.44 min, 253.4 $[M-H]^-$.

**Intermediate 1177:** 3,4-Difluoro-6-methyl-2-(6-methylhept-5-en-1-yl)phenyl trifluoromethanesulfonate

**[001335]** Prepared in an analogous manner to **Intermediate 414** using **Intermediate 1176** (0.76 g, 2.99 mmol), phenyl triflimide (1.17 g, 3.28 mmol, CAS 37595-74-7) and $Cs_2CO_3$ (1.17 g, 3.59 mmol) in DCM (30 mL) at RT for 5.5 h. Additional phenyl triflimide (1.0 g, 2.80 mmol) and $Cs_2CO_3$ (1.0 g, 3.07 mmol) were added and stirred at RT for 18 h. Purified by flash

chromatography (40 g silica gel, eluting 0–10% EtOAc in petroleum ether) to provide the title compound (0.98 g). $^1$H NMR (400 MHz; $CDCl_3$) δ: 7.00 – 6.91 (m, 1H), 5.13 – 5.05 (m, 1H), 2.81 – 2.73 (m, 2H), 2.35 (s, 3H), 2.00 (q, 2H), 1.68 (s, 3H), 1.62 – 1.50 (m, 5H), 1.44 – 1.33 (m, 2H).

**Intermediate 1178**: Ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(5-cyclopropyl-3',4,4'-trifluoro-6'-methyl-2'-(6-methylhept-5-en-1-yl)-[1,1'-biphenyl]-3-yl)propanoate

**[001336]** Prepared in an analogous manner to **Intermediate 3** using **Intermediate 1177** (0.88 g, 2.29 mmol), **Intermediate 377** (1.18 g, 2.30 mmol), $K_3PO_4$ (0.98 g, 4.59 mmol), palladium acetate (52 mg, 0.23 mmol) and SPhos (94 mg, 0.23 mmol) in toluene (13 mL) and water (2.5 mL) at 90 °C under microwave irradiation for 1 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether) to provide the title compound (1.08 g). LCMS (Method 15): 3.06 min, 586.3 $[M-H]^-$.

**Intermediate 1179:** Ethyl (*S*)-3-amino-3-(5-cyclopropyl-3',4,4'-trifluoro-6'-methyl-2'-(6-methylhept-5-en-1-yl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

**[001337]** A suspension of **Intermediate 1178** (1.08 g, 1.76 mmol) in 4 M HCl in 1,4-dioxane (4 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to provide the title compound (0.98 g). LCMS (Method 11): 2.76 min, 488.1 $[M+H]^+$.

**Intermediate 1180:** Ethyl (*S*)-3-(5-cyclopropyl-3',4,4'-trifluoro-6'-methyl-2'-(6-methylhept-5-en-1-yl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-hydroxypent-4-enamido)propanoate

**[001338]** Prepared in an analogous manner to **Intermediate 5** using **Intermediate 1179** (0.98 g, 1.88 mmol), (2*R*)-2-hydroxypent-4-enoic acid (0.23 g, 1.92 mmol, CAS 413622-10-3), DIPEA (1.0 mL, 5.74 mmol), HOBt (0.32 g, 1.90 mmol) and EDCI (0.48 g, 2.48 mmol) in MeCN (20 mL) at RT for 22 h. Purified by flash chromatography (25 g silica gel, eluting 0-5% MeOH in DCM) to provide the title compound (0.86 g). LCMS (Method 22): 2.83 min, 586.3 $[M+H]^+$.

**Intermediate 1181:** Ethyl (*S*)-3-(5-cyclopropyl-3',4,4'-trifluoro-6'-methyl-2'-(6-methylhept-5-en-1-yl)-[1,1'-biphenyl]-3-yl)-3-((*R*)-2-((methylsulfonyl)oxy)pent-4-enamido)propanoate

**[001339]** Prepared in an analogous manner to **Intermediate 56** using **Intermediate 1180** (0.86 g, 1.41 mmol), triethylamine (0.80 mL, 5.74 mmol) and methanesulfonyl chloride (0.80 mL, 10.3 mmol) in DCM (15 mL) at RT for 2 h, to provide the title compound (1.21 g). LCMS (Method 22): 2.86 min, 664.3 $[M+H]^+$.

**Intermediate 1182:** Ethyl (*S*)-3-(5-cyclopropyl-3',4,4'-trifluoro-6'-methyl-2'-(6-methylhept-5-en-1-yl)-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[001340]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 1181** (1.21 g, 1.41 mmol), **Intermediate 258** (0.37 g, 1.56 mmol) and $K_2CO_3$ (0.60 g, 4.34 mmol) in MeCN (5 mL) at reflux for 20 h. Additional **Intermediate 258** (0.15 g, 0.63 mmol) was added and stirred at reflux for 23 h. Purified by flash chromatography (40 g silica gel, eluting 0-4% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.22 g). LCMS (Method 21): 6.41 min, 802.4 $[M+H]^+$.

**Intermediate 1183:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^3$,1$^4$,2$^4$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001341]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1182** (0.20 g, 0.99 mmol) in DCE (15 mL) and Grubbs II (25 mg, 0.03 mmol) at 50 °C for 3 h. Conditions repeated. Purified by flash chromatography (24 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.17 g). LCMS (Method 21): 5.93 min, 746.4 $[M+H]^+$.

**Intermediate 1184:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^3$,1$^4$,2$^4$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001342]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1183** (0.17 g, 0.12 mmol) and 10% palladium on carbon (20 mg) in ethanol (5 mL) under a hydrogen atmosphere at RT for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (95 mg). LCMS (Method 21): 6.04 min, 748.4 $[M+H]^+$.

**Intermediate 1185:** Ethyl 2-((3*S*,6*S*)-6-(3-(2-(azetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001343]** Prepared in an analogous manner to **Intermediate 1107** using **Intermediate 714** (0.13 g, 0.17 mmol), in DCM (1.7 mL) and TFA (0.3 mL) at RT for 1 h. Then azetidine (11 µL, 0.21 mmol), triethylamine (71 µL, 0.51 mmol) in DCM (1.7 mL) with 4 Å molecular sieves at RT for 1 h, followed by STAB (0.14 g, 0.68 mmol) at RT for 72 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (42 mg). LCMS (Method 22): 2.91 min, 771.3 $[M+H]^+$.

**Intermediate 1186:** Ethyl 2-((3*S*,6*S*)-1$^4$,2$^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001344]** Prepared in an analogous manner to **Intermediate 1107** using **Intermediate 1164** (90 mg, 0.11 mmol), in DCM (2.5 mL) and TFA (0.17 mL) at RT for 4 h. Then 3-fluoroazetidine hydrochloride (8.3 mg, 0.11 mmol, CAS 617718-46-4), triethylamine (46 µL, 0.33 mmol) in DCM (2.5 mL) with 4 Å molecular sieves at RT for 1 h, followed by STAB (93 mg, 0.44 mmol) at RT for 80 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (60 mg). LCMS (Method 15): 2.76 min, 735.3 $[M+H]^+$.

**Intermediate 1187:** Ethyl (*S*)-3-((*S*)-2-(3-chloro-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)pent-4-enamido)-3-(5-cyclopropyl-2',4,4'-trifluoro-6'-(hex-5-en-1-yl)-[1,1'-biphenyl]-3-yl)propanoate

**[001345]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 739** (1.19 g, 1.63 mmol), **Intermediate 1137** (0.39 g, 1.95 mmol) and $K_2CO_3$ (0.67 g, 4.88 mmol) in MeCN (16 mL) at reflux for 2.5 h. Purified by flash chromatography (40 g silica gel, 0-30% EtOAc in petroleum ether) to provide the title compound (0.76 g). LCMS (Method 15): 2.89 min, 724.2 $[M+H]^+$.

**Intermediate 1188:** Ethyl 2-((3*S*,6*S*)-6-(3-chloro-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$1^6$,$2^4$-trifluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001346]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1187** (0.76 g, 0.94 mmol) in DCE (0.47 L) and Grubbs II (80 mg, 0.09 mmol) at 50 °C for 1.5 h. Purified by flash chromatography (24 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.45 g). LCMS (Method 15): 2.79 min, 696.2 $[M+H]^+$.

**Intermediate 1189:** Ethyl 2-((3*S*,6*S*)-6-(3-chloro-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$1^6$,$2^4$-trifluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001347]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1188** (0.45 g, 0.65 mmol) and 10% palladium on carbon (69 mg) in EtOAc (20 mL) under a hydrogen atmosphere at RT for 1.5 h, to provide the title compound (0.44 g). LCMS (Method 15): 2.83 min, 698.2 $[M+H]^+$.

**Intermediate 1190:** Ethyl 2-((3*S*,6*S*)-$2^5$-cyclopropyl-6-(3-((*E*)-2-ethoxyvinyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$1^6$,$2^4$-trifluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001348]** Prepared in an analogous manner to **Intermediate 364** using **Intermediate 1189** (0.40 g, 0.56 mmol), *trans*-2-ethoxyvinylboronic acid pinacol ester (0.24 g, 1.22 mmol,

CAS 1201905-61-4), Pd(dppf)$Cl_2$ (81 mg, 0.11 mmol) and $Na_2CO_3$ (0.12 g, 1.11 mmol) in toluene (5.7 mL) and water (2 mL) at 90 °C for 18 h. Additional *trans*-2-ethoxyvinylboronic acid pinacol ester (0.12 g, 0.61 mmol, CAS 1201905-61-4) and Pd(dppf)$Cl_2$ (41 mg, 56 µmol) added and heated at 90 °C for 1.5 h. Purified by flash chromatography (40 g silica gel, eluting 0-30% EtOAc in petroleum ether), to provide the title compound (0.24 g). LCMS (Method 15): 2.88 min, 734.3 $[M+H]^+$.

**Intermediate 1191:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(3-(2-(dimethylamino)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,1$^6$,2$^4$-trifluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001349]** Prepared in an analogous manner to **Intermediate 1107** using **Intermediate 1190** (0.24 g, 0.29 mmol), in DCM (14 mL) and TFA (0.88 mL) at RT for 3.5 h. Then dimethylamine (2 M in THF, 0.17 mL, 0.34 mmol), triethylamine (0.12 mL, 0.86 mmol) in DCM (14 mL) with 4 Å molecular sieves at RT for 1 h, followed by STAB (0.30 g, 1.43 mmol) at RT for 18 h. Purified by flash chromatography (25 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (85 mg). LCMS (Method 15): 2.80 min, 735.3 $[M+H]^+$.

**Intermediate 1192:** Ethyl 2-((3*S*,6*S*)-6-(3-(2-(azetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001350]** Prepared in an analogous manner to **Intermediate 1107** using **Intermediate 1164** (86 mg, 0.11 mmol), in DCM (2.5 mL) and TFA (0.17 mL) at RT for 4 h. Then azetidine (6.2 mg, 0.11 mmol), triethylamine (46 µL, 0.33 mmol) in DCM (2.5 mL) with 4 Å molecular sieves at RT for 1 h, followed by STAB (47 mg, 0.22 mmol) at RT for 16 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM), to provide the title compound (55 mg). LCMS (Method 15): 3.04 min, 717.3 $[M+H]^+$.

**Intermediate 1193:** Ethyl (*S*)-3-(5-cyclopropyl-4,4'-difluoro-2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyrimidin-1(2*H*)-yl)pent-4-enamido)propanoate

**[001351]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 508** (0.46 g, 0.75 mmol), 5-(2-(dimethylamino)ethyl)-4-methylpyrimidin-2(1*H*)-one (0.15 g, 0.82 mmol, CAS 2955527-96-3) and $K_2CO_3$ (0.31 g, 2.24 mmol) in MeCN (9 mL) at reflux for 16 h. Purified by flash chromatography (40 g silica gel, 0-10% MeOH in DCM) to provide the title compound (0.22 g). LCMS (Method 15): 2.68 min, 703.4 $[M+H]^+$.

**Intermediate 1194:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyrimidin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001352]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1193** (0.22 g, 0.31 mmol) in DCE (88 mL) and Grubbs II (27 mg, 0.03 mmol) at 50 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-10% MeOH in DCM) to provide the title compound (0.13 g). LCMS (Method 15): 2.57 min, 675.3 $[M+H]^+$.

**Intermediate 1195:** Ethyl 2-((3*S*,6*S*)-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyrimidin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001353]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1194** (0.12 g, 0.65 mmol) and 10% palladium on carbon (40 mg) in EtOAc (20 mL) under a hydrogen atmosphere at RT for 14 h, to provide the title compound (0.12 g). LCMS (Method 27): 2.83 min, 677.3 $[M+H]^+$.

**Intermediate 1196:** Methyl (*S*)-3-(2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)-3-((*S*)-2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)propanoate

**[001354]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 1039** (0.34 g, 0.65 mmol), **Intermediate 251** (0.13 g, 0.65 mmol) and $K_2CO_3$ (0.27 g, 1.94 mmol) in MeCN (8 mL) at 80 °C for 18 h. Purified by flash chromatography (24 g silica gel, eluting 2-7% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.22 g). LCMS (Method 15): 2.53 min, 640.4 $[M+H]^+$.

**Intermediate 1197:** Methyl 2-((3S,6S)-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

**[001355]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1196** (0.22 g, 0.34 mmol) in DCE (96 mL) and Grubbs II (29 mg, 34 µmol) at 40 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-6% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.20 g). LCMS (Method 15): 2.37 min, 612.3 $[M+H]^+$.

**Intermediate 1198:** Methyl 2-((3*S*,6*S*)-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001356]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1197** (0.20 g, 0.32 mmol) and 10% palladium on carbon (34 mg) in ethanol (7 mL) under a hydrogen atmosphere at RT for 16 h, to provide the title compound (0.15 g). LCMS (Method 15): 2.41 min, 614.3 $[M+H]^+$.

**Intermediate 1199:** Methyl (*S*)-3-((*S*)-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)pent-4-enamido)-3-(2'-(hex-5-en-1-yl)-6'-methyl-[1,1'-biphenyl]-3-yl)propanoate

**[001357]** Prepared in an analogous manner to **Intermediate 65** using **Intermediate 1039** (0.41 g, 0.78 mmol), **Intermediate 243** (0.15 g, 0.78 mmol) and $K_2CO_3$ (0.32 g, 2.35 mmol) in MeCN (10 mL) at 80 °C for 18 h. Purified by flash chromatography (24 g silica gel, eluting 2-7% (0.5% ammonia MeOH) in DCM) to provide the title compound (0.20 g). LCMS (Method 15): 2.58 min, 628.3 $[M+H]^+$.

**Intermediate 1200:** Methyl 2-((3*S*,6*S*)-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetate

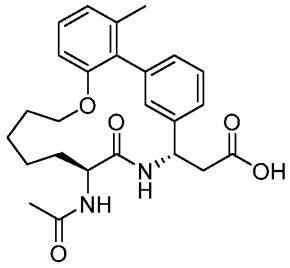
**[001358]** Prepared in an analogous manner to **Intermediate 7** using **Intermediate 1199** (0.20 g, 0.32 mmol) in DCE (89 mL) and Grubbs II (27 mg, 32 µmol) at 40 °C for 2 h. Purified by flash chromatography (12 g silica gel, eluting 0-6% (0.1% ammonia MeOH) in DCM) to provide the title compound (0.17 g). LCMS (Method 15): 2.41 min, 600.2 $[M+H]^+$.

**Intermediate 1201:** Methyl 2-((3*S*,6*S*)-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetate

**[001359]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 1200** (0.17 g, 0.28 mmol) and 10% palladium on carbon (29 mg) in ethanol (6 mL) under a hydrogen atmosphere at RT for 16 h, to provide the title compound (0.15 g). LCMS (Method 15): 2.47 min, 602.3 $[M+H]^+$.

**Synthesis of Examples**

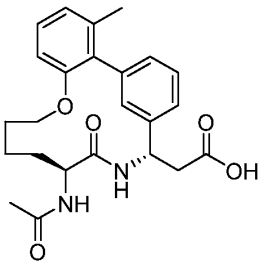
**Example 1:** 2-((9*S*,12*S*)-9-Acetamido-2$^6$-methyl-10-oxo-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid




**[001360]** **Intermediate 10** (0.15 g, 0.33 mmol) was dissolved in THF (3 mL) and water (1 mL) then lithium hydroxide (24 mg, 0.99 mmol) was added and the solution stirred at RT for 1 h. The mixture was concentrated under nitrogen stream then adjusted to pH 4 with 4M aqueous HCl. This was purified by reverse-phase chromatography (24 g C18, eluting 30-50% MeCN in water with 0.1% formic acid) to provide the title compound (66 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: Rotamer 1 (75%): 12.25 (br s, 1H), 8.76 (d, 1H), 7.96 (d, 1H), 7.29 (t, 1H),

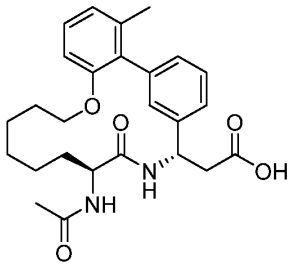
7.23 (s, 1H), 7.22 – 7.17 (m, 2H), 6.97 (d, 1H), 6.86 (d, 1H), 6.83 (d, 1H), 5.26 (q, 1H), 4.33 – 4.25 (m, 1H), 3.99 – 3.90 (m, 1H), 3.82 – 3.76 (m, 1H), 2.61 (dd, 1H), 2.54 (dd, 1H), 1.95 (s, 3H), 1.80 (s, 3H), 1.67 (m, 1H), 1.72 – 1.61 (m, 1H), 1.61 – 1.25 (m, 4H), 1.21 – 0.88 (m, 3H); Rotamer 2 (25%): 12.25 (br s, 1H), 8.45 (br d, 1H), 7.89 (d, 1H), 7.39 (t, 1H), 7.30 (d, 1H), 7.20 (t, 1H), 7.06 (s, 1H), 7.02 (d, 1H), 6.91 – 6.80 (m, 2H), 5.42 (q, 1H), 4.21 – 4.11 (br m, 1H), 3.89 – 3.82 (br m, 1H), 3.75 – 3.66 (br m, 1H), 2.97 (br dd, 1H), 2.81 (br dd, 1H), 1.96 (s, 3H), 1.80 (s, 3H), 1.70 – 1.60 (m, 1H), 1.58 – 1.22 (m, 3H), 1.21 – 0.87 (m, 4H). LCMS (Method 13): 1.75 min, 439.3 $[M+H]^+$.

**Example 2:** 2-((8*S*,11*S*)-8-Acetamido-2$^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid



**[001361]** Prepared in an analogous manner to **Example 1** using **Intermediate 15** (0.12 g, 0.28 mmol) and lithium hydroxide (20 mg, 0.83 mmol) in THF (3 mL) and water (1 mL) at RT for 1.5 h. Purified by reverse-phase chromatography (24 g C18, eluting 30-50% MeCN in water with 0.1% formic acid) to provide the title compound (67 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: 12.26 (br s, 1H), 8.82 (br s, 1H), 7.96 (d, 1H), 7.31 – 7.28 (m, 1H), 7.23 – 7.18 (m, 2H), 7.15 (s, 1H), 7.02 (d, 1H), 6.89 – 6.84 (m, 2H), 5.19 – 5.10 (br m, 1H), 4.31 – 4.22 (br m, 1H), 4.10 – 4.02 (br m, 1H), 3.68 – 3.59 (br m, 1H), 2.74 – 2.65 (m, 2H), 2.00 (s, 3H), 1.82 (s, 3H), 1.51 – 1.32 (m, 5H), 1.02 (br m, 1H). LCMS (Method 13): 1.65 min, 425.3 $[M+H]^+$.

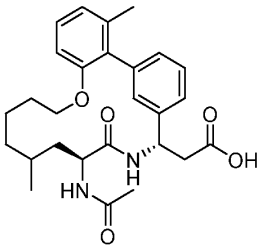
**Example 3:** 2-((10*S*,13*S*)-10-Acetamido-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001362]** Prepared in an analogous manner to **Example 1** using **Intermediate 20** (96 mg, 0.21 mmol) and lithium hydroxide (15 mg, 0.62 mmol) in THF (3 mL) and water (1 mL) at RT for 1.5 h. Purified by reverse-phase chromatography (24 g C18, eluting 30-50% MeCN in

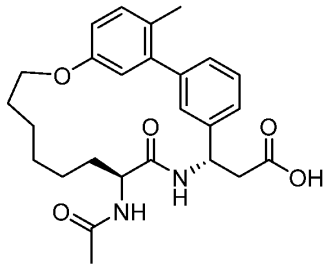
water with 0.1% formic acid) to provide the title compound (48 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: Rotamer 1 (75%): 12.20 (br s, 1H), 8.48 (br d, 1H), 7.85 (d, 1H), 7.27 (t, 1H), 7.24 – 7.16 (m, 3H), 7.00 (d, 1H), 6.92 (d, 1H), 6.89 (d, 1H), 5.29 (q, 1H), 4.30 – 4.22 (m, 1H), 3.98 – 3.93 (m, 1H), 3.83 – 3.74 (m, 1H), 2.76 (dd, 1H), 2.69 (dd, 1H), 1.94 (s, 3H), 1.82 (s, 3H), 1.46 – 1.26 (m, 4H), 1.10 – 0.80 (m, 5H), 0.69 – 0.57 (m, 1H). Rotamer 2 (25%): 12.20 (br s, 1H), 8.49 (br d, 1H), 7.85 (d, 1H), 7.44 – 7.17 (m, 4H), 7.10 – 6.97 (m, 2H), 6.96 – 6.85 (m, 1H), 5.29 (q, 1H), 4.22 – 4.11 (br m, 1H), 3.92 – 3.84 (br m, 1H), 3.77 – 3.65 (br m, 1H), 2.56 – 2.91 (m, 2H), 2.00 (s, 3H), 1.82 (s, 3H), 1.46 – 1.26 (m, 4H), 1.10 – 0.80 (m, 5H), 0.79 – 0.69 (m, 1H). LCMS (Method 11): 1.24 min, 453.3 $[M+H]^+$.

**Example 4:** 2-((10*S*,13*S*)-10-Acetamido-2$^6$,8-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001363]** Prepared in an analogous manner to **Example 1** using **Intermediate 26** (19 mg, 0.04 mmol) and lithium hydroxide (1 mg, 0.04 mmol) in THF (2 mL) and water (1 mL) at RT for 1 h. Purified by reverse-phase chromatography (20 g C18, eluting 40-80% MeCN in water with 0.1% formic acid) to provide the title compound (48 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: 12.07 (br s, 1H), 8.80 – 8.51 (br s, 1H), 8.14 – 7.86 (br d, 1H), 7.40 – 7.10 (m, 4H), 7.06 – 6.84 (m, 3H), 5.38 – 5.13 (m, 1H), 4.37 – 4.27 (m, 1H), 4.26 – 3.80 (m, 2H), 2.83 – 2.50 (m, 2H), 1.95 (s, 3H), 1.81 (s, 3H), 1.55 – 1.07 (m, 6H), 1.01 – 0.55 (m, 6H). LCMS (Method 15): 1.33 min, 467.2 $[M+H]^+$.

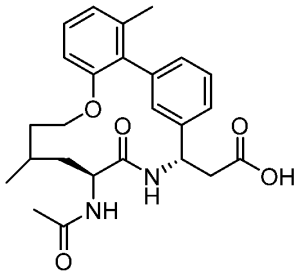
**Example 5:** 2-((10*S*,13*S*)-10-acetamido-2$^6$-methyl-11-oxo-3-oxa-12-aza-1,2(1,3)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001364]** **Intermediate 34** (37 mg, 0.08 mmol) was dissolved in THF (2 mL), MeOH (1 mL) and water (1 mL) then lithium hydroxide (5.7 mg, 0.24 mmol) was added and the solution

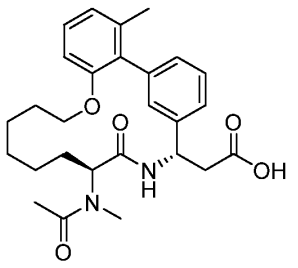
stirred at RT for 2 h. $NH_4Cl$ was added (21 mg, 0.40 mmol) and the mixture allowed to stand for 18 h. Solid was filtered and the filtrate concentrated under nitrogen. This was purified by flash chromatography (32 g silica, eluting 10-50% MeCN in water with 0.1% formic acid) and then by reverse-phase chromatography (24 g XBridge C18 30 mm x 250 mm 5uM, eluting 40-60% MeCN in water with 0.1% formic acid) to provide the title compound (6.4 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: 8.99 (br s, 1H), 7.93 (d, 1H), 7.36 – 7.26 (m, 2H), 7.24 (d, 1H), 7.20 – 7.15 (m, 2H), 6.87 (dd, 1H), 6.65 (d, 1H), 5.25 – 5.18 (m, 1H), 4.33 – 4.29 (m, 1H), 4.15 – 4.08 (m, 1H), 4.06 – 3.99 (m, 1H), 2.52 (dd, 1H), 2.51 (dd, 1H), 2.15 (s, 3H), 1.83 (s, 3H), 1.65 – 1.54 (m, 3H), 1.48 – 1.19 (m, 7H) – OH not observed. LCMS (Method 15): 1.32 min, 453.1 $[M+H]^+$.

**Example 6:** 2-((8*S*,11*S*)-8-Acetamido-2$^6$,6-dimethyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid



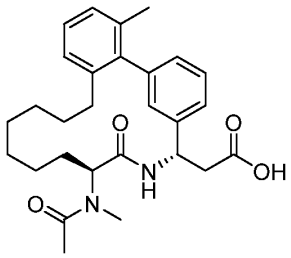
**[001365]** Prepared in an analogous manner to **Example 1** using **Intermediate 39** (30 mg, 0.07 mmol) and lithium hydroxide (4.8 mg, 0.20 mmol) in THF (2 mL) and water (1 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 10-30% MeCN in water with 0.1% ammonia over 20 min) to provide the title compound (5.9 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: 9.77 – 9.00 (br s, 1H), 8.11 – 7.87 (br d, 1H), 7.33 – 7.05 (m, 4H), 7.04 – 6.82 (m, 2H), 6.77 – 6.67 (d, 1H), 5.32 – 4.86 (m, 2H), 4.56 – 4.26 (m, 1H), 4.02 – 3.72 (m, 1H), 2.63 – 2.50 (m, 2H), 2.40 – 1.93 (m, 6H), 1.84 (s, 3H), 1.55 – 0.81 (m, 5H) – OH not observed. LCMS (Method 15): 1.33 min, 439.2 $[M+H]^+$.

**Example 7:** 2-((10*S*,13*S*)-2$^6$-Methyl-10-(*N*-methylacetamido)-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



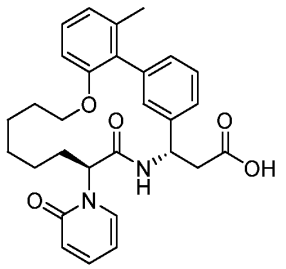
**[001366]** Prepared in an analogous manner to **Example 1** using **Intermediate 45** (80 mg, 0.17 mmol) and lithium hydroxide (12 mg, 0.50 mmol) in THF (2 mL) and water (1 mL) at RT for 1.5 h. Purified by reverse phase chromatography (20 g C18, eluting 30-70% MeCN in water with 0.1% formic acid) to provide the title compound (31 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: 11.93 (br s, 1H), 8.72 – 8.53 (br s, 1H), 7.30 – 7.19 (m, 4H), 7.12 – 6.87 (m, 3H), 5.29 – 5.21 (m, 1H), 4.93 – 4.65 (m, 1H), 4.13 – 3.56 (m, 2H), 2.97 (s, 3H), 2.73 – 2.54 (m, 2H), 2.01 (s, 3H), 1.99 (s, 3H), 1.81 – 1.52 (m, 1H), 1.46 – 1.29 (m, 3H), 1.22 – 0.89 (m, 6H). LCMS (Method 4): 1.05 min, 467.2 $[M+H]^+$.

**Example 8:** 2-((3*S*,6*S*)-1$^6$-Methyl-6-(*N*-methylacetamido)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001367]** Prepared in an analogous manner to **Example 5** using **Intermediate 52** (77 mg, 0.16 mmol) and lithium hydroxide monohydrate (20 mg, 0.48 mmol) in THF (2 mL), MeOH (1 mL) and water (1 mL) at RT for 2 h. Purified by reverse phase chromatography (20 g C18, eluting 20-70% MeCN in 0.1% aqueous formic acid) to provide the title compound (22 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: 12.25 (br s, 1H), 8.82 – 8.62 (d, 1H), 7.48 – 7.29 (m, 2H), 7.23 – 7.05 (m, 4H), 7.01 – 6.92 (m, 1H), 5.45 – 5.22 (m, 1H), 4.94 – 3.96 (dd, 1H), 2.91 – 2.75 (s, 3H), 2.66 – 2.55 (m, 2H), 2.39 – 2.24 (m, 2H), 2.07 – 1.76 (m, 7H), 1.32 – 0.76 (m, 11H). LCMS (Method 15): 1.49 min, 465.3 $[M+H]^+$.

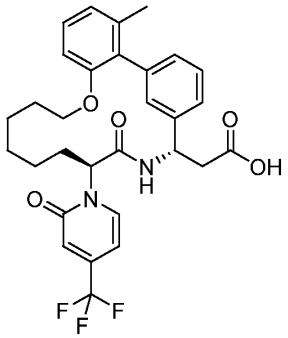
**Example 9:** 2-((10*S*,13*S*)-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001368]** Prepared in an analogous manner to **Example 1** using **Intermediate 59** (75 mg, 0.15 mmol) and lithium hydroxide (11 mg, 0.45 mmol) in THF (2 mL), MeOH (1 mL) and water (1 mL) at RT for 2 h. Purified by reverse phase chromatography (40 g C18, eluting 10-

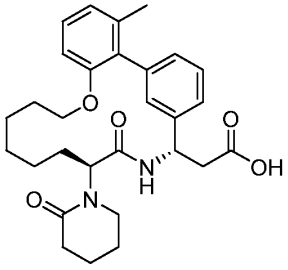
70% MeCN in 0.1% aqueous formic acid) to provide the title compound (10 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: 12.30 (br s, 1H), 9.08 (br s, 1H), 7.85 (dd, 1H), 7.43 – 7.36 (m, 1H), 7.32 – 7.26 (m, 3H), 7.18 – 6.97 (m, 2H), 6.96 – 6.87 (m, 2H), 6.37 (d, 1H), 6.26 – 6.20 (m, 1H), 5.46 – 5.40 (m, 1H), 5.26 – 5.22 (m, 1H), 3.95 – 3.91 (m, 1H), 3.89 – 3.85 (m, 1H), 2.89 – 2.66 (m, 2H), 1.92 (s, 3H), 1.73 – 1.69 (m, 1H), 1.47 – 1.37 (m, 3H), 1.26 – 1.23 (m, 1H), 1.19 – 1.15 (m, 1H), 1.01 – 0.85 (m, 4H). LCMS (Method 16): 3.95 min, 489.2 $[M+H]^+$.

**Example 10:** 2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001369]** Prepared in an analogous manner to **Example 1** using **Intermediate 62** (100 mg, 0.18 mmol) and lithium hydroxide (13 mg, 0.53 mmol) in THF (2 mL), MeOH (1 mL) and water (1 mL) at RT for 2 h. Purified by reverse phase chromatography (40 g C18, eluting 10-70% MeCN in 0.1% aqueous formic acid) to provide the title compound (28 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: 12.23 (br s, 1H), 9.11 (s, 1H), 8.12 (d, 1H), 7.45 – 7.15 (m, 4H), 7.11 – 6.87 (m, 3H), 6.78 (s, 1H), 6.51 – 6.46 (m, 1H), 5.43 – 5.38 (m, 1H), 5.27 – 5.24 (m, 1H), 3.95 – 3.86 (m, 2H), 2.88 – 2.66 (m, 2H), 1.96 (s, 3H), 1.77 – 1.69 (m, 1H), 1.56 – 1.33 (m, 3H), 1.28 – 1.12 (m, 2H), 1.03 – 0.86 (m, 4H). LCMS (Method 8): 2.14 min, 557.5 $[M+H]^+$.

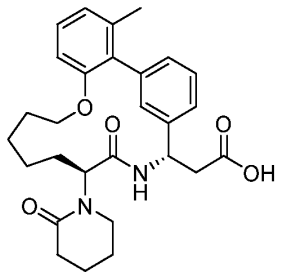
**Example 11:** 2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxopiperidin-1-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001370]** Prepared in an analogous manner to **Intermediate 8** using **Example 9** (30 mg, 0.06 mmol) and platinum oxide (1.4 mg) in MeOH (2 mL) under a hydrogen atmosphere at RT for 5 h, to provide the title compound (15 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: 12.00 (br s,

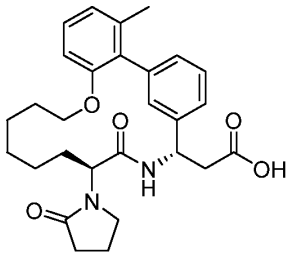
1H), 8.56 (d, 1H), 7.30 – 7.15 (m, 4H), 7.00 – 6.86 (m, 3H), 5.27 – 5.18 (m, 1H), 4.96 – 4.90 (m, 1H), 3.91 – 3.84 (m, 2H), 2.79 – 2.63 (m, 2H), 2.59 – 2.53 (m, 2H), 2.28 – 2.22 (m, 2H), 1.92 (s, 3H), 1.69 – 1.58 (m, 4H), 1.48 – 1.37 (m, 2H), 1.26 – 1.11 (m, 2H), 1.02 – 0.95 (m, 6H). LCMS (Method 8): 1.95 min, 493.5 $[M+H]^+$.

**Example 12:** 2-((9*S*,12*S*)-2$^6$-Methyl-10-oxo-9-(2-oxopiperidin-1-yl)-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid



**[001371]** Prepared in an analogous manner to **Example 1** using **Intermediate 67** (15 mg, 0.03 mmol) and lithium hydroxide (0.7 mg, 0.03 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by reverse phase chromatography (32 g C18, eluting 10-60% MeCN in 0.1% aqueous formic acid) to provide the title compound (10 mg). $^1$H NMR (500 MHz; $CD_3OD$) δ: 7.35 – 7.24 (m, 3H), 7.16 (dd, 1H), 7.01 (d, 1H), 6.83 (d, 1H), 6.79 (d, 1H), 5.37 (dd, 1H), 5.15 (dd, 1H), 3.93 – 3.87 (m, 1H), 3.84 – 3.80 (m, 1H), 3.45 – 3.40 (m, 1H), 3.38 – 3.32 (m, 1H), 2.73 – 2.64 (m, 2H), 2.44 – 2.33 (m, 2H), 2.10 – 2.04 (m, 1H), 2.03 (s, 3H), 1.83 – 1.73 (m, 5H), 1.53 – 1.22 (m, 6H). LCMS (Method 7): 1.92 min, 479.3 $[M+H]^+$.

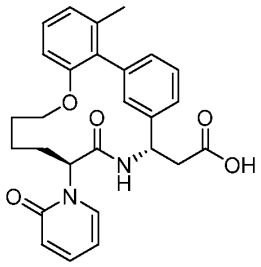
**Example 13:** 2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxopyrrolidin-1-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001372]** To a solution of **Intermediate 72** (12 mg, 18.1 µmol) in DMF (1 mL) was added DIPEA (3.2 µL, 18.1 µmol), HOBt (2.4 mg, 18.1 µmol) and EDCI (3.8 mg, 19.9 µmol) and the mixture was stirred at RT for 15 h. To this was added water (1 mL) and lithium hydroxide (3.5 mg, 0.14 mmol) and stirred at RT for 2 h. The mixture was acidified to pH 4 with 2 M aqueous HCl then purified by reverse phase chromatography (32 g C18, eluting 0 - 60% MeCN in 0.1% aqueous formic acid) to provide the title compound (3.4 mg). $^1$H NMR (500 MHz; $CD_3OD$) δ: 7.40 – 7.29 (m, 2H), 7.24 – 7.16 (m, 2H), 7.10 – 7.03 (m, 1H), 6.89 – 6.84 (m, 2H), 5.43 (t,

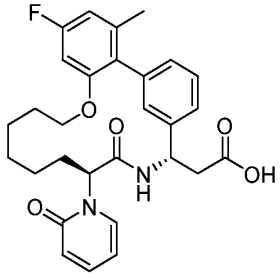
1H), 4.51 – 4.38 (m, 1H), 3.95 – 3.91 (m, 1H), 3.85 – 3.74 (m, 2H), 3.53 – 3.49 (m, 1H), 2.98 – 2.79 (m, 2H), 2.38 – 2.35 (m, 2H), 2.05 – 1.98 (m, 2H), 1.98 (s, 3H), 1.80 – 1.79 (m, 1H), 1.49 – 1.37 (m, 4H), 1.29 – 1.05 (m, 5H). LCMS (Method 7): 1.94 min, 479.3 $[M+H]^+$.

**Example 14:** 2-((8*S*,11*S*)-2$^6$-Methyl-9-oxo-8-(2-oxopyridin-1(2*H*)-yl)-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid



**[001373]** Prepared in an analogous manner to **Example 1** using **Intermediate 79** (100 mg, 0.21 mmol) and lithium hydroxide (15 mg, 0.63 mmol) in THF (3 mL), MeOH (1.5 mL) and water (1.5 mL) at RT for 5 h. Purified by reverse phase chromatography (40 g C18, eluting 20-70% MeCN in 0.1% aqueous formic acid) to provide the title compound (35 mg). $^1$H NMR (500 MHz; $CD_3OD$) δ: 7.92 (dd, 1H), 7.55 – 7.48 (m, 1H), 7.37 – 7.29 (m, 2H), 7.28 – 7.24 (m, 1H), 7.23 – 7.16 (m, 1H), 7.09 – 7.04 (m, 1H), 6.88 (d, 1H), 6.82 (d, 1H), 6.54 (dd, 1H), 6.44 – 6.37 (m, 1H), 5.55 – 5.48 (m, 1H), 5.28 – 5.22 (m, 1H), 4.15 – 4.10 (m, 1H), 3.79 – 3.72 (m, 1H), 2.92 (dd, 1H), 2.75 (dd, 1H), 2.08 (s, 3H), 2.01 – 1.91 (m, 1H), 1.78 – 1.65 (m, 3H), 1.67 – 1.53 (m, 1H), 1.41 – 1.31 (m, 1H). LCMS (Method 7): 1.78 min, 461.2 $[M+H]^+$.

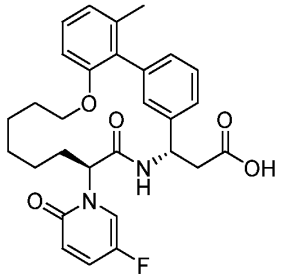
**Example 15:** 2-((10*S*,13*S*)-2$^4$-fluoro-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001374]** Prepared in an analogous manner to **Example 1** using **Intermediate 87** (20 mg, 0.04 mmol) and lithium hydroxide (2.8 mg, 0.12 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 2 h. Purified by reverse phase chromatography (32 g C18, eluting 20-70% MeCN in 0.1% aqueous formic acid) to provide the title compound (7 mg). $^1$H NMR (500 MHz; $CD_3OD$) δ: 7.78 (dd, 1H), 7.43 – 7.32 (m, 1H), 7.29 – 7.19 (m, 1H), 7.17 – 7.11 (m, 1H), 7.10 – 7.00 (m, 1H), 7.00 – 6.93 (m, 1H), 6.58 – 6.49 (m, 2H), 6.45 – 6.39 (m, 1H), 6.33 – 6.26 (m, 1H), 5.40 – 5.15 (m, 2H), 3.90 – 3.83 (m, 1H), 3.79 – 3.62 (m, 1H), 2.90 – 2.71 (m,

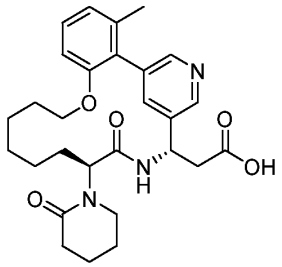
2H), 1.99 –1.74 (m, 4H), 1.54 – 1.34 (m, 3H), 1.29 – 0.74 (m, 6H). LCMS (Method 7): 2.03 min, 507.2 $[M+H]^+$.

**Example 16:** 2-((10*S*,13*S*)-10-(5-Fluoro-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



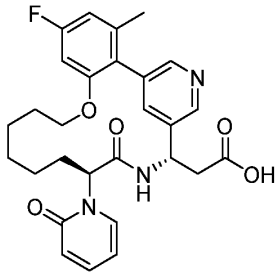
**[001375]** Prepared in an analogous manner to **Example 1** using **Intermediate 90** (10 mg, 0.02 mmol) and lithium hydroxide (0.5 mg, 0.02 mmol) in THF (0.5 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 4 h. Purified by reverse phase chromatography (32 g C18, eluting 20-60% MeCN in 0.1% aqueous formic acid) to provide the title compound (2.4 mg). $^1$H NMR (500 MHz; $CD_3OD$) δ: 7.99 – 7.91 (m, 1H), 7.58 – 7.49 (m, 1H), 7.48 – 7.27 (m, 3H), 7.23 – 7.04 (m, 2H), 6.91 – 6.83 (m, 2H), 6.53 (dd, 1H), 5.52 – 5.28 (m, 2H), 4.03 – 3.96 (m, 1H), 3.89 – 3.70 (m, 1H), 3.04 – 2.82 (m, 2H), 2.09 – 1.85 (m, 4H), 1.67 – 1.45 (m, 3H), 1.38 – 1.20 (m, 2H), 1.19 – 1.03 (m, 4H). LCMS (Method 7): 2.04 min, 507.2 $[M+H]^+$.

**Example 17:** 2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxopiperidin-1-yl)-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetic acid



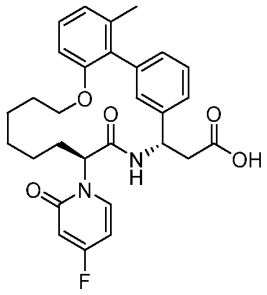
**[001376]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 100** (8 mg, 0.06 mmol) and platinum oxide (0.5 mg) in MeOH (1 mL) under a hydrogen atmosphere at RT for 3 h, to provide the title compound (7 mg). $^1$H NMR (500 MHz; $CD_3OD$) δ: 8.55 (s, 1H), 8.21 (s, 1H), 7.74 (s, 1H), 7.25 (t, 1H), 6.92 (d, 2H), 5.45 (t, 1H), 4.98 – 4.93 (m, 1H), 3.99 – 3.96 (m, 1H), 3.89 – 3.84 (m, 1H), 3.69 – 3.67 (m, 1H), 3.36 (dd, 1H), 2.94 – 2.85 (m, 1H), 2.47 – 2.32 (m, 2H), 2.01 (s, 3H), 1.88 – 1.77 (m, 5H), 1.52 – 1.48 (m, 2H), 1.41 – 1.01 (m, 8H). LCMS (Method 7): 1.55 min, 494.2 $[M+H]^+$.

**Example 18:** 2-((10*S*,13*S*)-2$^4$-Fluoro-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetic acid



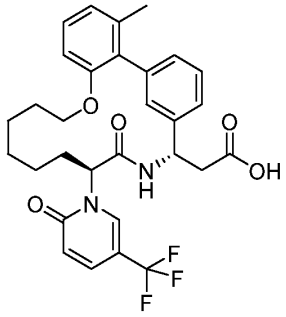
**[001377]** Prepared in an analogous manner to **Example 1** using **Intermediate 110** (50 mg, 0.09 mmol) and lithium hydroxide (6.7 mg, 0.28 mmol) in THF (2 mL), MeOH (1 mL) and water (1 mL) at RT for 2 h. Purified by reverse phase chromatography (46 g C18, eluting 10-60% MeCN in 0.1% aqueous formic acid) to provide the title compound (14 mg). $^1$H NMR (500 MHz; $CD_3OD$) δ: 8.61 – 8.58 (m, 1H), 8.25 – 8.21 (m, 1H), 7.92 (d, 1H), 7.80 – 7.76 (m, 1H), 7.52 (t, 1H), 6.77 – 6.66 (m, 2H), 6.57 – 6.52 (m, 1H), 6.46 – 6.39 (m, 1H), 5.53 – 5.33 (m, 2H), 4.04 – 4.01 (m, 1H), 3.93 – 3.87 (m, 1H), 2.97 – 2.94 (m, 2H), 2.09 –1.87 (m, 5H), 1.66 – 1.50 (m, 2H), 1.42 – 1.27 (m, 2H), 1.25 – 1.15 (m, 2H), 1.11 – 1.00 (m, 2H). LCMS (Method 8): 1.60 min, 508.5 $[M+H]^+$.

**Example 19:** 2-((10*S*,13*S*)-10-(4-Fluoro-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



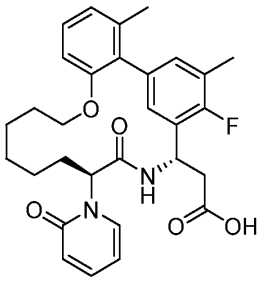
**[001378]** Prepared in an analogous manner to **Example 1** using **Intermediate 117** (10 mg, 0.02 mmol) and lithium hydroxide (0.5 mg, 0.02 mmol) in THF (0.5 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 4 h. Purified by reverse phase chromatography (32 g C18, eluting 20-60% MeCN in 0.1% aqueous formic acid) to provide the title compound (3 mg). $^1$H NMR (500 MHz; $CD_3OD$) δ: 8.01 – 7.75 (m, 1H), 7.42 (s, 1H), 7.35 – 7.28 (m, 2H), 7.20 – 7.13 (m, 1H), 7.06 – 7.04 (d, 1H), 6.88 – 6.84 (m, 2H), 6.34 – 5.89 (m, 2H), 5.52 – 5.21 (m, 2H), 4.01 – 3.93 (m, 1H), 3.88 – 3.69 (m, 1H), 3.01 – 2.98 (m, 1H), 2.91 – 2.84 (m, 1H), 2.09 – 1.79 (m, 4H), 1.66 – 1.41 (m, 3H), 1.38 – 1.27 (m, 1H), 1.25 – 0.99 (m, 5H). LCMS (Method 7): 1.95 min, 507.2 $[M+H]^+$.

**Example 20:** 2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxo-5-(trifluoromethyl)pyridin-1(2H)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



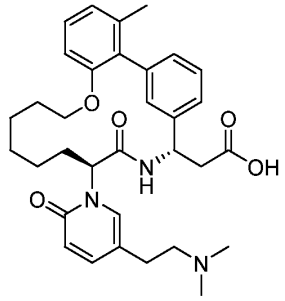
**[001379]** Prepared in an analogous manner to **Example 1** using **Intermediate 120** (80 mg, 0.14 mmol) and lithium hydroxide (3.4 mg, 0.14 mmol) in THF (3 mL), MeOH (1.5 mL) and water (1.5 mL) at RT for 5 h. Purified by reverse phase chromatography (32 g C18, eluting 10-40% MeCN in 0.1% aqueous formic acid) to provide the title compound (29 mg). $^1$H NMR (400 MHz; $CD_3OD$) δ: 8.31 (d, 1H), 7.65 (dd, 1H), 7.49 – 7.32 (m, 2H), 7.31 – 7.05 (m, 3H), 6.88 (d, 2H), 6.62 (d, 1H), 5.56 – 5.33 (m, 2H), 4.06 – 3.93 (m, 1H), 3.90 – 3.70 (m, 1H), 3.03 – 2.80 (m, 2H), 2.11 – 1.85 (m, 4H), 1.65 – 1.44 (m, 3H), 1.41 – 1.29 (m, 1H), 1.28 – 0.85 (m, 5H). LCMS (Method 7): 2.07 min, 557.2 $[M+H]^+$.

**Example 21:** 2-((10*S*,13*S*)-1$^4$-Fluoro-1$^5$,2$^6$-dimethyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



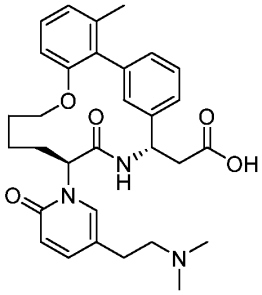
**[001380]** Prepared in an analogous manner to **Example 1** using **Intermediate 134** (97 mg, 0.18 mmol) and lithium hydroxide (13 mg, 0.53 mmol) in THF (3 mL), MeOH (1 mL) and water (1 mL) at RT for 2.5 h. Purified by reverse phase chromatography (32 g C18, eluting 20-55% MeCN in 0.1% aqueous formic acid) to provide the title compound (8 mg). $^1$H NMR (400 MHz; DMSO-$d_6$) δ: 12.27 (br s, 1H), 9.19 (br s, 1H), 7.85 (dd, 1H), 7.39 (dt, 1H), 7.21 (t, 1H), 7.18 – 7.11 (m, 1H), 6.95 (d, 1H), 6.88 (d, 2H), 6.37 (dd, 1H), 6.23 (dt, 1H), 5.71 – 5.59 (m, 1H), 5.44 (t, 1H), 3.99 – 3.88 (m, 2H), 2.55 – 2.50 (m, 2H), 2.24 (s, 3H), 1.92 (s, 3H), 1.83 – 1.76 (m, 1H), 1.52 – 1.40 (m, 3H), 1.32 – 1.20 (m, 2H), 1.13 – 0.97 (m, 4H). LCMS (Method 8): 2.01 min, 521.4 $[M+H]^+$.

**Example 22:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



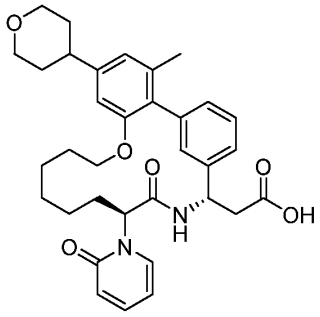
**[001381]** Prepared in an analogous manner to **Example 1** using **Intermediate 140** (67 mg, 0.08 mmol) and lithium hydroxide (3.9 mg, 0.16 mmol) in THF (0.7 mL), MeOH (0.4 mL) and water (0.4 mL) at RT for 3 h. Purified by reverse phase chromatography (32 g C18, eluting 5-35% MeCN in 0.1% aqueous ammonia) to provide the title compound (41 mg). $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.79 (s, 1H), 7.44 – 7.39 (m, 2H), 7.34 – 7.25 (m, 2H), 7.16 (t, 1H), 7.00 (d, 1H), 6.86 (d, 2H), 6.48 (d, 1H), 5.52 – 5.30 (m, 2H), 4.00 – 3.93 (m, 1H), 3.86 – 3.79 (m, 1H), 2.91 – 2.64 (m, 2H), 2.64 – 2.58 (m, 2H), 2.55 – 2.47 (m, 2H), 2.30 (s, 6H), 1.99 (s, 3H), 1.95 – 1.86 (m, 1H), 1.58 – 1.44 (m, 3H), 1.35 – 1.21 (m, 2H), 1.18 – 1.02 (m, 4H). LCMS (Method 11): 1.40 min, 560.4 $[M+H]^+$.

**Example 23:** 2-((8*S*,11*S*)-8-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid



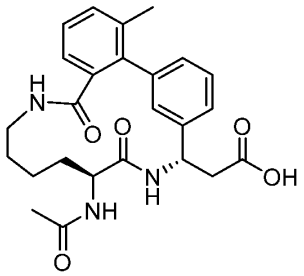
**[001382]** Prepared in an analogous manner to **Example 1** using **Intermediate 143** (12 mg, 0.02 mmol) and lithium hydroxide (2.6 mg, 0.11 mmol) in THF (1 mL), MeOH (1 mL) and water (0.5 mL) at RT for 45 min. Purified by reverse phase chromatography (20 g C18, eluting 2-50% MeCN in 0.1% aqueous ammonia) to provide the title compound (4.3 mg). $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.81 (d, 1H), 7.43 (dd, 1H), 7.38 – 7.32 (m, 1H), 7.32 – 7.26 (m, 2H), 7.16 (dd, 1H), 7.00 (d, 1H), 6.84 (d, 1H), 6.79 (d, 1H), 6.48 (d, 1H), 5.53 (d, 1H), 5.23 – 5.17 (m, 1H), 4.10 (d, 1H), 3.74 (t, 1H), 2.89 – 2.58 (m, 4H), 2.56 – 2.50 (m, 2H), 2.31 (s, 6H), 2.05 (s, 3H), 1.96 – 1.89 (m, 1H), 1.75 – 1.52 (m, 4H), 1.39 –1.30 (m, 1H). LCMS (Method 8): 1.42 min, 530.5 $[M-H]^-$.

**Example 24:** 2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-2$^4$-(tetrahydro-2*H*-pyran-4-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



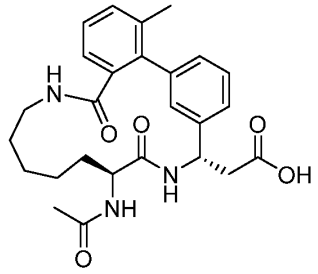
**[001383]** Prepared in an analogous manner to **Example 1** using **Intermediate 153** (63 mg, 0.11 mmol) and lithium hydroxide (7.8 mg, 0.33 mmol) in THF (8.3 mL), MeOH (5 mL) and water (5 mL) at RT for 5 h. Purified by reverse phase chromatography (32 g C18, eluting 5-70% MeCN in 0.1% aqueous formic acid) to provide the title compound (11 mg). $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.89 (d, 1H), 7.53 – 7.46 (m, 1H), 7.45 – 7.17 (m, 3H), 7.04 (d, 1H), 6.82 – 6.72 (m, 2H), 6.54 (d, 1H), 6.45 – 6.34 (m, 1H), 5.52 – 5.26 (m, 2H), 4.12 – 4.03 (m, 2H), 4.02 – 3.64 (m, 2H), 3.59 (td, 2H), 3.00 – 2.72 (m, 3H), 2.09 – 1.88 (m, 4H), 1.86 – 1.71 (m, 3H), 1.64 – 1.42 (m, 3H), 1.39 – 0.90 (m, 7H). LCMS (Method 16): 4.20 min, 573.1 $[M+H]^+$.

**Example 25:** 2-((3*S*,6*S*)-6-Acetamido-1$^6$-methyl-5,12-dioxo-4,11-diaza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



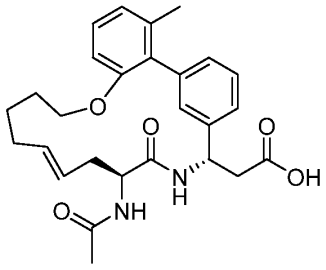
**[001384]** Prepared in an analogous manner to **Example 1** using **Intermediate 162** (20 mg, 0.04 mmol) and lithium hydroxide (3.1 mg, 0.13 mmol) in THF (1 mL) and water (1 mL) at RT for 1.5 h. Purified by reverse phase chromatography (20 g C18, eluting 20-60% MeCN in 0.1% aqueous formic acid) to provide the title compound (19 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: 12.20 (br s, 1H), 8.67 – 8.37 (br d, 1H), 7.95 – 7.80 (d, 1H), 7.61 – 7.43 (m, 1H), 7.37 – 7.25 (m, 3H), 7.21 (t, 1H), 7.12 (s, 1H), 7.07 – 7.01 (m, 2H), 5.41 – 5.16 (q, 1H), 4.21 – 4.12 (m, 1H), 3.15 – 3.02 (m, 1H), 2.95 – 2.84 (m, 1H), 2.82 – 2.59 (m, 2H), 2.00 – 1.92 (s, 3H), 1.81 (s, 3H), 1.46 – 1.23 (m, 2H), 1.17 – 0.95 (m, 2H), 0.91 – 0.62 (m, 2H). LCMS (Method 15): 0.92 min, 452.1 $[M+H]^+$.

**Example 26:** 2-((3*S*,6*S*)-6-Acetamido-1$^6$-methyl-5,13-dioxo-4,12-diaza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001385]** Prepared in an analogous manner to **Example 1** using **Intermediate 169** (32 mg, 0.07 mmol) and lithium hydroxide (4.8 mg, 0.20 mmol) in THF (1.5 mL) and water (1 mL) at RT for 1 h. Purified by reverse phase chromatography (20 g C18, eluting 30-70% MeCN in 0.1% aqueous formic acid) to provide the title compound (24 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: Rotamer 1 (70%): 12.16 (br s, 1H), 8.09 (d, 1H), 7.99 (d, 1H), 7.37 – 7.26 (m, 5H), 7.23 (d, 1H), 7.02 – 6.98 (m, 2H), 5.26 (q, 1H), 4.26 – 4.19 (m, 1H), 3.25 – 3.22 (m, 1H), 2.74 (d, 2H), 2.71 – 2.53 (m, 2H), 2.02 (s, 3H), 1.81 (s, 3H), 1.65 – 1.58 (m, 1H), 1.42 –1.36 (m, 1H), 1.23 – 1.18 (m, 1H), 1.14 – 1.03 (m, 2H), 0.80 – 0.60 (m, 2H); Rotamer 2 (30%): 12.16 (br s, 1H), 8.66 (d, 1H), 7.85 (d, 1H), 7.48 (d, 1H), 7.37 – 7.26 (m, 5H), 7.13 (s, 1H), 7.07 (d, 1H), 5.26 (q, 1H), 4.26 – 4.19 (m, 1H), 3.25 – 3.22 (m, 1H), 3.05 – 3.01 (m, 1H), 2.71 – 2.53 (m, 2H), 2.06 (s, 3H), 1.81 (s, 3H), 1.65 – 1.58 (m, 1H), 1.52 – 1.48 (m, 1H), 1.14 – 1.03 (m, 2H), 0.99 – 0.94 (m, 1H), 0.75 – 0.57 (m, 2H), 0.52 – 0.47 (m, 1H). LCMS (Method 15): 0.97 min, 466.2 $[M+H]^+$.

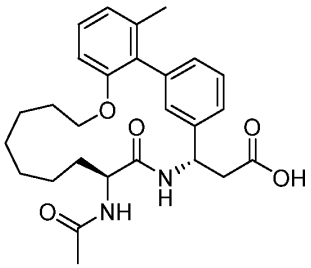
**Example 27:** 2-((11*S*,14*S*,*E*)-11-Acetamido-2$^6$-methyl-12-oxo-3-oxa-13-aza-1(1,3),2(1,2)-dibenzenacyclotetradecaphan-8-en-14-yl)acetic acid



**[001386]** **Intermediate 175** (28 mg, 0.06 mmol) was dissolved in THF (1 mL), MeOH (0.5 mL) and water (0.5 mL) then lithium hydroxide monohydrate (12 mg, 0.29 mmol) was added and the solution stirred at RT for 2 h. The mixture was diluted with water then adjusted to pH 3 with 4M aqueous HCl then extracted with DCM. The organic layer was concentrated under reduced pressure. The crude residue was purified by reverse-phase chromatography (20 g C18, eluting 0-50% MeCN in water with 0.1% formic acid) to provide the title compound

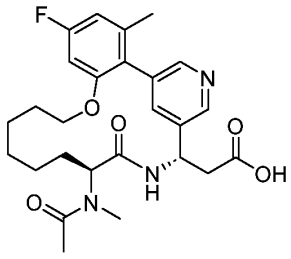
(12 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: 12.06 (br s, 1H), 8.68 (br s, 1H) 8.58 – 8.52 (m, 1H), 8.04 – 7.87 (m, 1H), 7.48 – 7.39 (m, 1H), 7.29 – 7.16 (m, 2H), 7.06 – 6.99 (m, 1H), 6.90 (d, 2H), 5.35 – 5.10 (m, 2H), 5.02 – 4.89 (m, 1H), 4.36 – 4.13 (m, 1H), 4.00 – 3.94 (m, 1H), 3.81 – 3.62 (m, 1H), 2.78 – 2.57 (m, 2H), 2.24 – 2.13 (m, 2H), 1.97 (s, 3H), 1.84 (s, 3H), 1.68 – 1.32 (m, 4H), 1.03 – 0.93 (m, 2H). LCMS (Method 7): 1.91 min, 465.2 $[M+H]^+$.

**Example 28:** 2-((11*S*,14*S*)-11-Acetamido-2$^6$-methyl-12-oxo-3-oxa-13-aza-1(1,3),2(1,2)-dibenzenacyclotetradecaphane-14-yl)acetic acid



**[001387]** Prepared in an analogous manner to **Example 27** using **Intermediate 178** (68 mg, 0.14 mmol) and lithium hydroxide monohydrate (30 mg, 0.71 mmol) in THF (2.4 mL), MeOH (1.2 mL) and water (1.2 mL) at RT for 2 h. Purified by reverse phase chromatography (20 g C18, eluting 0-50% MeCN in 0.1% aqueous formic acid) to provide the title compound (50 mg). $^1$H NMR (500 MHz; DMSO-$d_6$) δ: 12.11 (br s, 1H), 8.72 – 8.64 (m, 1H), 7.96 – 7.88 (m, 1H), 7.48 – 7.36 (m, 1H), 7.29 – 7.23 (m, 1H), 7.20 – 7.17 (m, 1H), 7.03 – 6.98 (m, 1H), 6.96 – 6.83 (m, 3H), 5.35 – 5.18 (m, 1H), 4.26 – 4.12 (m, 1H), 3.94 – 3.69 (m, 2H), 2.80 – 2.62 (m, 2H), 1.97 (s, 3H), 1.80 (s, 3H), 1.51 – 1.30 (m, 4H), 1.18 – 0.73 (m, 8H). LCMS (Method 7): 1.98 min, 467.2 $[M+H]^+$.

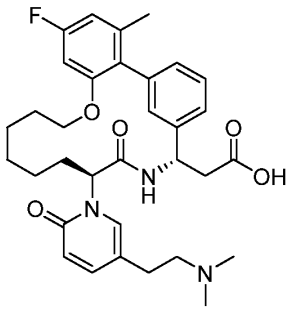
**Example 29:** 2-((10*S*,13*S*)-2$^4$-Fluoro-2$^6$-methyl-10-(*N*-methylacetamido)-11-oxo-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetic acid



**[001388]** Prepared in an analogous manner to **Example 27** using **Intermediate 186** (49 mg, 0.10 mmol) and lithium hydroxide monohydrate (12 mg, 0.29 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.3 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 10-40% MeCN in water with 0.1% ammonia over 15 min) to provide the title compound (3 mg). $^1$H NMR (400 MHz; $CD_3OD$) δ: 8.61 – 8.58 (m, 1H), 8.19 (s, 1H), 7.77

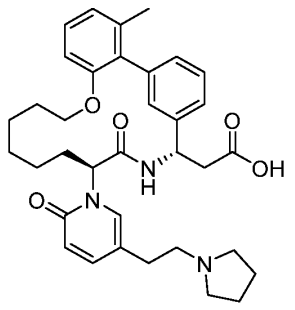
– 7.74 (m, 1H), 6.73 – 6.65 (m, 2H), 5.43 (t, 1H), 4.54 – 4.51 (m, 1H), 4.04 – 3.72 (m, 2H), 3.21 – 2.90 (m, 3H), 2.86 – 2.67 (m, 2H), 2.23 – 1.90 (m, 6H), 1.86 – 1.39 (m, 3H) 1.37 – 0.74 (m, 7H). LCMS (Method 15): 1.25 min, 486.2 $[M+H]^+$.

**Example 30:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001389]** Prepared in an analogous manner to **Example 1** using **Intermediate 189** (15 mg, 0.02 mmol) and lithium hydroxide (1.6 mg, 0.07 mmol) in THF (0.4 mL), MeOH (0.2 mL) and water (0.2 mL) at RT for 2 h. Purified by reverse phase chromatography (32 g C18, eluting 10-30% MeCN in 0.1% aqueous formic acid) to provide the title compound (10 mg). $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.82 – 7.72 (m, 1H), 7.47 (d, 1H), 7.37 – 7.30 (m, 2H), 7.28 – 7.22 (m, 1H), 7.04 – 7.00 (m, 1H), 6.68 (d, 1H), 6.62 (d, 1H), 6.54 (d, 1H), 5.57 – 5.39 (m, 2H), 3.97 – 3.77 (m, 2H), 3.24 – 3.15 (m, 2H), 2.88 – 2.55 (m, 9H), 2.11 – 1.99 (m, 4H), 1.60 – 1.56 (m, 3H), 1.41 – 1.10 (m, 7H). LCMS (Method 16): 3.18 min, 578.2 $[M+H]^+$.

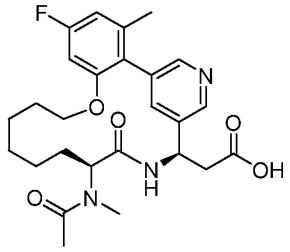
**Example 31:** 2-((10*S*,13*S*)-$2^6$-Methyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001390]** Prepared in an analogous manner to **Example 1** using **Intermediate 193** (35 mg, 0.05 mmol) and lithium hydroxide (3.4 mg, 0.14 mmol) in THF (0.6 mL), MeOH (0.4 mL) and water (0.4 mL) at RT for 1 h. Purified by reverse phase chromatography (32 g C18, eluting 10-35% MeCN in 0.1% aqueous ammonia) to provide the title compound (20 mg). $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.81 (br s, 1H), 7.45 (d, 1H), 7.40 – 7.25 (m, 3H), 7.17 (t, 1H), 7.09 – 7.00 (m, 1H), 6.90 – 6.82 (m, 2H), 6.52 (d, 1H), 5.60 – 5.37 (m, 2H), 3.97 – 3.91 (m, 1H), 3.87

– 3.72 (m, 1H), 3.20 – 3.00 (m, 6H), 2.77 (t, 2H), 2.66 – 2.57 (m, 1H), 2.06 – 1.93 (m, 8H), 1.59 – 1.43 (m, 3H), 1.37 – 1.04 (m, 7H). LCMS (Method 14): 3.04 min, 586.2 $[M+H]^+$.

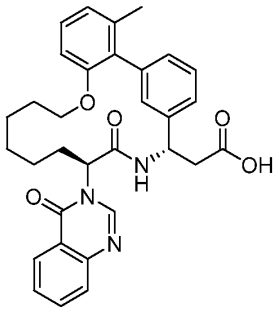
**Example 32:** 2-((10*S*,13*R*)-2$^4$-Fluoro-2$^6$-methyl-10-(*N*-methylacetamido)-11-oxo-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetic acid



**[001391]** Prepared in an analogous manner to **Example 27** using **Intermediate 186** (49 mg, 0.10 mmol) and lithium hydroxide monohydrate (12 mg, 0.29 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.3 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 10-40% MeCN in water with 0.1% ammonia over 15 min) to provide the title compound (3 mg). $^1$H NMR (400 MHz; $CD_3OD$) δ: 8.60 – 8.47 (m, 1H), 8.24 – 8.16 (m, 1H), 7.92 – 7.87 (m, 1H), 6.73 – 6.62 (m, 2H), 5.43 (t, 1H), 4.54 – 4.51 (m, 1H), 4.04 – 3.72 (m, 2H), 3.13 – 2.75 (m, 5H), 2.23 – 1.90 (m, 6H), 1.59 – 1.47 (m, 3H) 1.39 – 0.79 (m, 7H). LCMS (Method 15): 1.16 min, 486.2 $[M+H]^+$.

**[001392]** Examples 33-66 were prepared in an analogous manner to Examples 1-32:

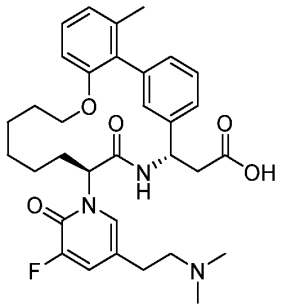
**Example 33:** 2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(4-oxoquinazolin-3(4*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001393]** Prepared in an analogous manner to **Example 27** using **Intermediate 196** (0.12 g, 0.22 mmol) and lithium hydroxide monohydrate (16 mg, 0.65 mmol) in THF (2 mL), MeOH (1 mL) and water (1 mL) at RT for 2 h. Purified by reverse phase chromatography (C18 40 g, eluting 10-70% MeCN in 0.1% aqueous formic acid over 30 min) to provide the title compound (70 mg). $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 12.22 (br s, 1H), 9.10 (d, 1H), 8.51 (s, 1H), 8.16 (dd, 1H), 7.85 (t, 1H), 7.70 (d, 1H), 7.56 (t, 1H), 7.43 – 7.39 (m, 1H), 7.35– 7.19 (m, 3H), 7.08 – 7.00 (m, 1H), 6.94 (d, 1H), 6.90 (d, 1H), 5.46 – 5.39 (m, 1H), 5.31 – 5.23 (m, 1H),

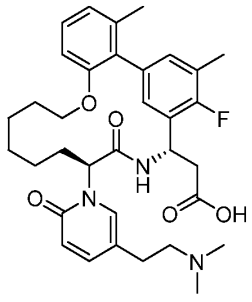
3.96 – 3.92 (m, 1H), 3.90 – 3.87 (m, 1H), 2.86 – 2.78 (m, 1H), 2.77 – 2.69 (m, 1H), 2.04 – 1.84 (m, 4H), 1.65 – 1.58 (m, 1H), 1.52 – 1.48 (m, 1H), 1.44 – 1.37 (m, 1H), 1.28 – 0.97 (m, 6H). LCMS (Method 7): 2.05 min, 540.2 $[M+H]^+$.

**Example 34:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001394]** Prepared in an analogous manner to **Example 27** using **Intermediate 203** (17 mg, 0.03 mmol) and lithium hydroxide monohydrate (1.0 mg, 0.04 mmol) in THF (1 mL), MeOH (1 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 15-40% MeCN in 0.1% aqueous ammonia over 10 min) to provide the title compound (3.8 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.69 (s, 1H), 7.39 – 7.27 (m, 4H), 7.21 – 7.17 (m, 1H), 7.09 – 7.02 (m, 1H), 6.93 – 6.88 (m, 2H), 5.59 – 5.45 (m, 2H), 3.99 – 3.85 (m, 2H), 3.19 – 3.03 (m, 2H), 2.85 – 2.78 (m, 2H), 2.73 (s, 6H), 2.67 – 2.58 (m, 1H), 2.13 – 1.99 (m, 4H), 1.60 – 1.47 (m, 3H), 1.39 – 1.10 (m, 7H). LCMS (Method 15): 1.31 min, 578.2 $[M+H]^+$.

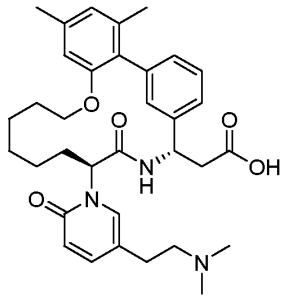
**Example 35:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001395]** Prepared in an analogous manner to **Example 27** using **Intermediate 210** (43 mg, 0.07 mmol) and lithium hydroxide monohydrate (2.5 mg, 0.10 mmol) in THF (1 mL), MeOH (1 mL) and water (0.5 mL) at RT for 1 h. Purified by reverse phase chromatography (C18 32 g, eluting 5-50% MeCN in 0.1% aqueous ammonia) followed by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 15-45% MeCN in 0.1% aqueous formic acid over 10 min) to

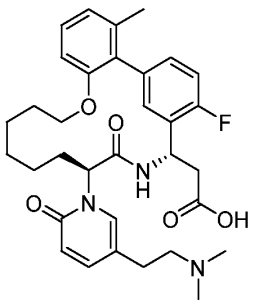
provide the title compound (11 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.63 (s, 1H), 7.39 (d, 1H), 7.07 (dd, 1H), 7.00 (d, 1H), 6.78 (dd, 3H), 6.45 (d, 1H), 5.79 (dd, 1H), 5.40 – 5.37 (m, 1H), 3.94 – 3.70 (m, 3H), 2.90 – 2.40 (m, 9H), 2.19 (s, 3H), 2.05 – 1.98 (m, 2H), 1.90 (s, 3H), 1.51 – 1.30 (m, 4H), 1.29 – 1.08 (m, 6H). LCMS (Method 15): 1.35 min, 592.2 $[M+H]^+$.

**Example 36:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001396]** Prepared in an analogous manner to **Example 27** using **Intermediate 218** (80 mg, 0.14 mmol) and lithium hydroxide monohydrate (10 mg, 0.41 mmol) in THF (2 mL), MeOH (0.8 mL) and water (0.8 mL) at RT for 2 h. Purified by reverse phase chromatography (C18 32 g, eluting 5-30% MeCN in 0.1% aqueous ammonia) followed by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 20-40% MeCN in water with 0.1% aqueous ammonia over 15 min) to provide the title compound (6.4 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.88 – 7.80 (m, 1H), 7.52 – 7.45 (m, 1H), 7.41 – 7.22 (m, 3H), 7.11 – 7.00 (m, 1H), 6.77 – 6.67 (m, 2H), 6.56 (d, 1H), 5.62 – 5.39 (m, 2H), 3.98 – 3.75 (m, 2H), 3.25 – 3.12 (m, 2H), 2.90 – 2.73 (m, 8H), 2.67 – 2.54 (m, 1H), 2.34 (s, 3H), 2.16 – 2.05 (m, 1H), 2.00 (s, 3H), 1.61 – 1.44 (m, 3H), 1.44 – 1.10 (m, 7H). LCMS (Method 15): 1.43 min, 574.2 $[M+H]^+$.

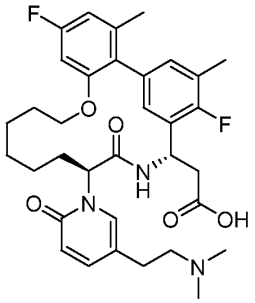
**Example 37:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001397]** Prepared in an analogous manner to **Example 27** using **Intermediate 231** (17 mg, 0.03 mmol) and lithium hydroxide monohydrate (2.0 mg, 0.08 mmol) in THF (0.6 mL), MeOH (0.4 mL) and water (0.4 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 20-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide

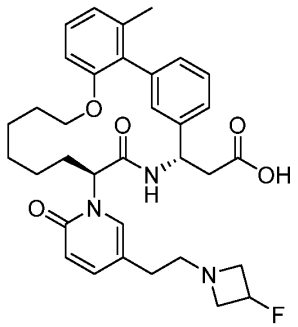
the title compound (6.1 mg). $^1$H NMR (500 MHz, $CD_3OD$) δ: 7.75 (s, 1H), 7.47 (dd, 1H), 7.33 – 7.28 (m, 1H), 7.18 (dd, 1H), 7.10 (dd, 1H), 7.04 (s, 1H), 6.92 – 6.87 (m, 2H), 6.55 (d, 1H), 5.93 – 5.87 (m, 1H), 5.58 – 5.51 (m, 1H), 3.97 – 3.78 (m, 2H), 3.24 – 3.17 (m, 1H), 2.85 – 2.71 (m, 8H), 2.61 – 2.54 (m, 1H), 2.47 – 2.40 (m, 1H), 2.24 – 2.13 (m, 1H), 2.03 (s, 3H), 1.57 – 1.47 (m, 4H), 1.47 – 1.22 (m, 6H). LCMS (Method 15): 1.35 min, 578.2 $[M+H]^+$.

**Example 38:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001398]** Prepared in an analogous manner to **Example 27** using **Intermediate 242** (30 mg, 0.03 mmol) and lithium hydroxide (2 M aqueous, 20 µL, 0.04 mmol) in THF (1 mL) and MeOH (1 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 23 min) to provide the title compound (7.2 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.72 (s, 1H), 7.47 (dd, 1H), 7.09 (d, 1H), 6.88 (d, 1H), 6.68 (d, 1H), 6.61 (dd, 1H), 6.54 (d, 1H), 5.95 – 5.78 (m, 1H), 5.53 (dd, 1H), 3.98 – 3.84 (m, 2H), 3.22 – 3.08 (m, 2H), 2.90 – 2.50 (m, 4H), 2.72 (s, 6H), 2.50 – 2.40 (m, 1H), 2.29 (s, 3H), 2.22 – 2.09 (m, 1H), 2.01 (s, 3H), 1.68 – 1.20 (m, 8H). LCMS (Method 8): 1.57 min, 610.4 $[M+H]^+$.

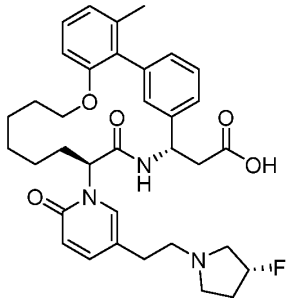
**Example 39:** 2-((10*S*,13*S*)-10-(5-(2-(3-Fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001399]** Prepared in an analogous manner to **Example 27** using **Intermediate 246** (54 mg, 0.09 mmol) and lithium hydroxide (6.4 mg, 0.27 mmol) in THF (1 mL), MeOH (0.5 mL)

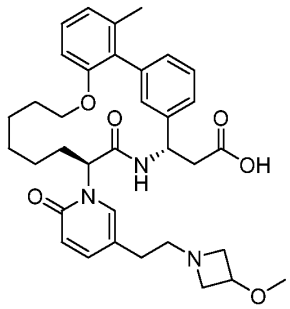
and water (0.5 mL) at RT for 1 h. Purified by reverse phase chromatography (C18 32 g, eluting 10-30% MeCN in 0.1% aqueous ammonia) to provide the title compound (27 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.70 (s, 1H), 7.44 (d, 1H), 7.38 – 7.32 (m, 2H), 7.30 – 7.22 (m, 1H), 7.18 (dd, 1H), 7.11 – 7.02 (m, 1H), 6.91 – 6.83 (m, 2H), 6.52 (d, 1H), 5.54 – 5.39 (m, 2H), 5.33 – 5.13 (m, 1H), 4.15 – 3.99 (m, 2H), 3.88 – 3.82 (m, 1H), 3.77 – 3.61 (m, 2H), 3.09 (dd, 2H), 2.88 – 2.81 (m, 1H), 2.72 – 2.55 (m, 3H), 2.10 – 1.96 (m, 4H), 1.60 – 1.07 (m, 10H). LCMS (Method 11): 1.30 min, 590.4 $[M+H]^+$.

**Example 40:** 2-((10*S*,13*S*)-10-(5-(2-((*R*)-3-Fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



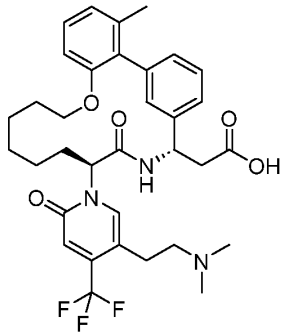
**[001400]** Prepared in an analogous manner to **Example 27** using **Intermediate 250** (72 mg, 0.11 mmol) and lithium hydroxide (7.8 mg, 0.33 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by reverse phase chromatography (C18 32 g, eluting 10-30% MeCN in 0.1% aqueous ammonia) to provide the title compound (36 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.79 (s, 1H), 7.46 (d, 1H), 7.41 – 7.31 (m, 2H), 7.28 – 7.22 (m, 1H), 7.18 (dd, 1H), 7.11 – 7.01 (m, 1H), 6.92 – 6.83 (m, 2H), 6.52 (d, 1H), 5.54 – 5.42 (m, 2H), 5.38 – 5.34 (m, 1H), 5.25 – 5.20 (m, 1H), 3.97 – 3.91 (m, 1H), 3.87 – 3.72 (m, 2H), 3.17 – 3.04 (m, 3H), 2.88 – 2.82 (m, 1H), 2.79 – 2.62 (m, 3H), 2.39 – 2.15 (m, 3H), 2.06 – 1.96 (m, 4H), 1.58 – 1.42 (m, 3H), 1.37 – 1.05 (m, 6H). LCMS (Method 15): 0.95 min, 604.2 $[M+H]^+$.

**Example 41:** 2-((10*S*,13*S*)-10-(5-(2-(3-Methoxyazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



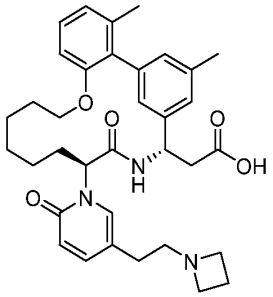
**[001401]** Prepared in an analogous manner to **Example 27** using **Intermediate 254** (40 mg, 0.07 mmol) and lithium hydroxide (4.7 mg, 0.20 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by reverse phase chromatography (C18 32 g, eluting 5-30% MeCN in 0.1% aqueous ammonia) to provide the title compound (10 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.69 (s, 1H), 7.44 (d, 1H), 7.38 – 7.25 (m, 3H), 7.17 (dd, 1H), 7.09 – 7.00 (m, 1H), 6.90 – 6.82 (m, 2H), 6.52 (d, 1H), 5.57 – 5.39 (m, 2H), 4.25 – 4.10 (m, 3H), 3.95 – 3.77 (m, 2H), 3.71 – 3.55 (m, 2H), 3.24 – 3.19 (m, 2H), 2.79 – 2.52 (m, 4H), 2.11 – 1.99 (m, 4H), 1.58 – 1.42 (m, 3H), 1.39 – 1.09 (m, 6H) - OMe obscured by solvent peak. LCMS (Method 15): 1.34 min, 602.2 $[M+H]^+$.

**Example 42:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



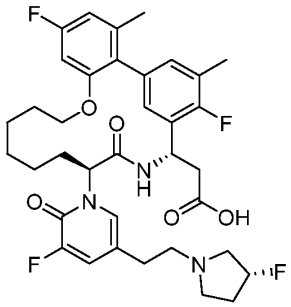
**[001402]** Prepared in an analogous manner to **Example 27** using **Intermediate 261** (35 mg, 0.06 mmol) and lithium hydroxide (2M aqueous, 33 µL, 66 µmol) in THF (1 mL) and MeOH (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (11.5 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.02 (s, 1H), 7.50 – 7.21 (m, 3H), 7.14 (dd, 1H), 7.10 – 6.97 (m, 1H), 6.91 – 6.85 (m, 2H), 6.80 (s, 1H), 5.57 – 5.32 (m, 2H), 4.01 – 3.92 (m, 1H), 3.88 – 3.67 (m, 1H), 2.93 – 2.48 (m, 6H), 2.37 (s, 6H), 2.14 – 1.84 (m, 4H), 1.64 – 1.45 (m, 3H), 1.42 – 0.82 (m, 6H). LCMS (Method 16): 2.95 min, 628.2 $[M+H]^+$.

**Example 43:** 2-((10*S*,13*S*)-10-(5-(2-(Azetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



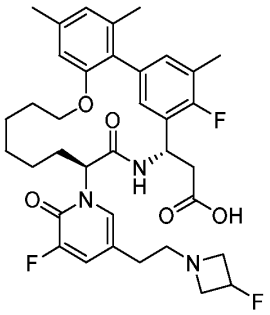
**[001403]** Prepared in an analogous manner to **Example 27** using **Intermediate 275** (10 mg, 12 µmol) and lithium hydroxide (2M aqueous, 7 µL, 14 µmol) in THF (5 mL), MeOH (0.5 mL) and water (0.1 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (3.2 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.76 (s, 1H), 7.41 (dd, 1H), 7.34 – 7.21 (m, 1H), 7.18 – 7.01 (m, 2H), 6.94 – 6.77 (m, 3H), 6.48 (d, 1H), 5.56 – 5.32 (m, 2H), 3.99 – 3.91 (m, 1H), 3.89 – 3.69 (m, 1H), 3.27 – 3.17 (m, 3H), 2.92 – 2.55 (m, 4H), 2.51 – 2.27 (m, 5H), 2.17 – 1.84 (m, 6H), 1.52 (s, 3H), 1.42 – 0.78 (m, 7H). LCMS (Method 7): LCMS (Method 7): 1.43 min, 586.3 $[M+H]^+$.

**Example 44:** 2-((10*S*,13*S*)-1$^4$,2$^4$-Difluoro-10-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



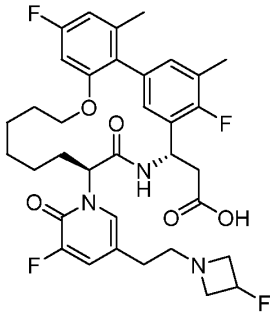
**[001404]** Prepared in an analogous manner to **Example 27** using **Intermediate 280** (80 mg, 0.11 mmol) and lithium hydroxide (8.2 mg, 0.34 mmol) in THF (2.5 mL), MeOH (1.5 mL) and water (1.5 mL) at RT for 1.5 h. Purified by reverse phase chromatography (C18 20 g, eluting 0-60% MeCN in 0.1% aqueous formic acid) to provide the title compound (44 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.55 (s, 1H), 7.36 (dd, 1H), 7.07 (d, 1H), 6.89 (d, 1H), 6.69 (d, 1H), 6.62 (dd, 1H), 5.89 – 5.80 (m, 1H), 5.56 – 5.48 (m, 1H), 5.38 – 5.24 (m, 1H), 3.97 – 3.91 (m, 3H), 2.84 – 2.79 (m, 2H), 2.62 – 2.43 (m, 3H), 2.38 – 2.12 (m, 8H), 2.01 (s, 3H), 1.59 – 1.42 (m, 4H), 1.41 – 1.22 (m, 7H). LCMS (Method 7): LCMS (Method 7): 1.58 min, 672.2 $[M+H]^+$.

**Example 45:** 2-((10*S*,13*S*)-1$^4$-Fluoro-10-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001405]** Prepared in an analogous manner to **Example 27** using **Intermediate 290** (22 mg, 0.03 mmol) and lithium hydroxide (2M aqueous, 24 µL, 48 µmol) in THF (1 mL) and MeOH (1 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-45% MeCN in 0.1% aqueous ammonia over 10 min) to provide the title compound (5 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.61 (s, 1H), 7.30 (d, 1H), 7.12 (d, 1H), 6.85 (d, 1H), 6.69 (s, 2H), 5.86 – 5.82 (m, 1H), 5.53 – 5.48 (m, 1H), 5.18 – 5.02 (m, 1H), 4.00 – 3.83 (m, 2H), 3.73 – 3.53 (m, 2H), 3.28 – 3.19 (m, 2H), 2.78 – 2.54 (m, 4H), 2.52 – 2.48 (m, 2H), 2.31 (s, 3H), 2.28 (s, 3H), 2.03 – 1.94 (m, 4H), 1.67 – 1.09 (m, 9H). LCMS (Method 15): 1.36 min, 654.4 $[M+H]^+$.

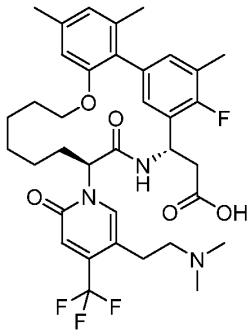
**Example 46:** 2-((10*S*,13*S*)-1$^4$,2$^4$-Difluoro-10-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001406]** Prepared in an analogous manner to **Example 27** using **Intermediate 293** (47 mg, 0.07 mmol) and lithium hydroxide (4.9 mg, 0.21 mmol) in THF (1 mL), MeOH (0.4 mL) and water (0.4 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 25-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (9 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.50 (s, 1H), 7.35 (dd, 1H), 7.11 (d, 1H), 6.91 (d, 1H), 6.75 – 6.67 (m, 1H), 6.63 (dd, 1H), 5.89 (dd, 1H), 5.57 (dd, 1H), 5.37 – 5.15 (m,

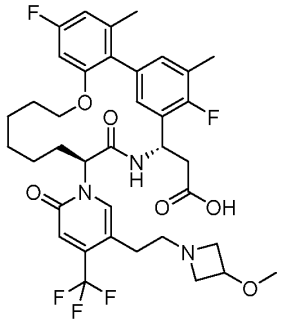
1H), 4.25 – 4.06 (m, 2H), 4.02 – 3.90 (m, 2H), 3.89 – 3.70 (m, 2H), 3.21 – 3.13 (m, 2H), 2.73 – 2.60 (m, 3H), 2.58 – 2.47 (m, 1H), 2.32 (s, 3H), 2.21 – 2.09 (m, 1H), 2.03 (s, 3H), 1.62 – 1.50 (m, 3H), 1.47 – 1.22 (m, 6H). LCMS (Method 20): 3.30 min, 658.5 $[M+H]^+$.

**Example 47:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-$1^4$-fluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001407]** Prepared in an analogous manner to **Example 27** using **Intermediate 296** (26 mg, 36 µmol) and lithium hydroxide (1.3 mg, 55 µmol) in THF (1 mL), MeOH (1 mL) and water (0.5 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 15-45% MeCN in 0.1% aqueous ammonia over 10 min) to provide the title compound (9.1 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.02 (s, 1H), 7.14 (d, 1H), 6.86 (d, 1H), 6.83 (s, 1H), 6.71 (s, 2H), 5.88 (dd, 1H), 5.52 (dd, 1H), 4.01 – 3.96 (m, 1H), 3.92 – 3.82 (m, 1H), 2.84 – 2.56 (m, 6H), 2.41 (s, 6H), 2.33 (s, 3H), 2.30 (s, 3H), 2.07 – 1.94 (m, 4H), 1.65 – 1.08 (m, 9H). LCMS (Method 24): 3.38 min, 674.2 $[M+H]^+$.

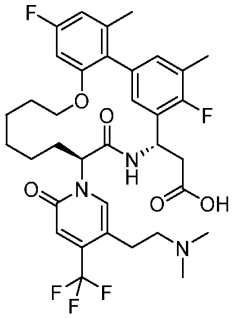
**Example 48:** 2-((10*S*,13*S*)-$1^4$,$2^4$-Difluoro-10-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001408]** Prepared in an analogous manner to **Example 27** using **Intermediate 301** (34 mg, 46 µmol) and lithium hydroxide (2.2 mg, 91 µmol) in THF (1 mL), MeOH (1 mL) and water (0.5 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting

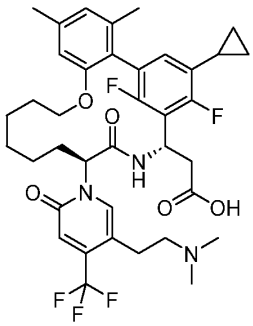
15-45% MeCN in 0.1% aqueous ammonia over 10 min) to provide the title compound (8.4 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.99 (s, 1H), 7.15 (d, 1H), 6.86 (d, 1H), 6.81 (s, 1H), 6.67 (d, 1H), 6.61 (d, 1H), 5.86 (dd, 1H), 5.52 (dd, 1H), 4.09 – 3.97 (m, 2H), 3.94 – 3.88 (m, 1H), 3.68 – 3.56 (m, 2H), 3.25 (s, 3H), 3.08 – 3.04 (m, 2H), 2.83 – 2.56 (m, 5H), 2.30 (s, 3H), 2.07 – 1.97 (m, 4H), 1.68 – 1.15 (m, 10H). LCMS (Method 21): 3.24 min, 720.2 $[M+H]^+$.

**Example 49:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



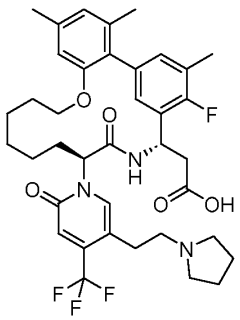
**[001409]** Prepared in an analogous manner to **Example 27** using **Intermediate 308** (66 mg, 94 μmol) and lithium hydroxide (6.7 mg, 0.28 mmol) in THF (2 mL), MeOH (1.2 mL) and water (1.2 mL) at RT for 1.5 h. Purified by reverse phase chromatography (32 g C18, 5-100% MeCN in 0.1% aqueous ammonia) to provide the title compound (3.3 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.03 (s, 1H), 7.10 (d, 1H), 6.88 – 6.84 (m, 2H), 6.69 (d, 1H), 6.62 (d, 1H), 5.95 (dd, 1H), 5.50 (dd, 1H), 3.97 – 3.89 (m, 2H), 3.18 – 2.83 (m, 4H), 2.67 (s, 6H), 2.66 – 2.42 (m, 2H), 2.29 (s, 3H), 2.17 – 1.96 (m, 4H), 1.68 – 1.53 (m, 3H), 1.46 – 1.15 (m, 6H). LCMS (Method 21): 3.24 min, 678.2 $[M+H]^+$.

**Example 50:** 2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^2$,1$^4$-difluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



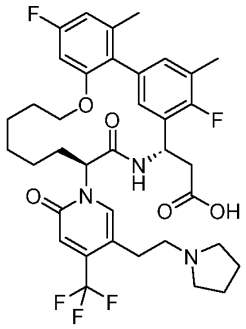
**[001410]** Prepared in an analogous manner to **Example 27** using **Intermediate 321** (0.10 g, 0.13 mmol) and lithium hydroxide (13 mg, 0.57 mmol) in THF (1.3 mL), MeOH (1.3 mL) and water (1.3 mL) at RT for 2 h. Purified by reverse phase chromatography (32 g C18, 5-50% MeCN in 0.1% aqueous ammonia) then preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (18 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.06 (s, 1H), 6.82 (s, 1H), 6.71 – 6.55 (m, 3H), 6.00 – 5.92 (m, 1H), 5.54 (dd, 1H), 3.97 – 3.90 (m, 2H), 3.03 – 2.69 (m, 6H), 2.54 (s, 6H), 2.32 (s, 3H), 2.10 – 2.00 (m, 2H), 1.94 (s, 3H), 1.68 – 0.91 (m, 11H), 0.71 – 0.58 (m, 2H). LCMS (Method 29): 3.52 min, 718.6 $[M+H]^+$.

**Example 51:** 2-((10*S*,13*S*)-1$^4$-Fluoro-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



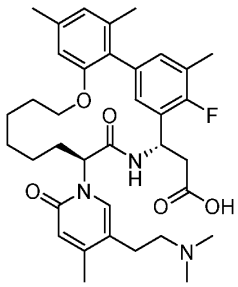
**[001411]** Prepared in an analogous manner to **Example 27** using **Intermediate 327** (71 mg, 74 µmol) and lithium hydroxide (2.7 mg, 0.11 mmol) in THF (0.8 mL), MeOH (0.4 mL) and water (0.4 mL) at RT for 1 h. Purified by reverse phase chromatography (32 g C18, 20-50% MeCN in 0.1% aqueous ammonia) then preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 10 min) to provide the title compound (14 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.03 (s, 1H), 7.13 (d, 1H), 6.93 – 6.85 (m, 2H), 6.72 (s, 2H), 5.90 – 5.87 (m, 1H), 5.54 – 5.51 (m, 1H), 3.97 – 3.90 (m, 2H), 2.98 – 2.53 (m, 9H), 2.34 – 2.24 (m, 6H), 2.03 – 1.90 (m, 8H), 1.66 – 1.01 (m, 10H). LCMS (Method 19): 3.25 min, 700.3 $[M+H]^+$.

**Example 52:** 2-((10*S*,13*S*)-1$^4$,2$^4$-Difluoro-1$^5$,2$^6$-dimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



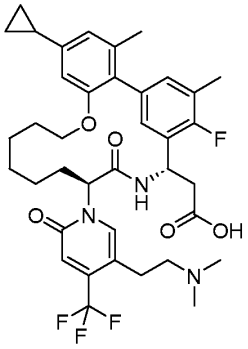
**[001412]** Prepared in an analogous manner to **Example 27** using **Intermediate 330** (0.10 g, 0.10 mmol) and lithium hydroxide (3.7 mg, 0.16 mmol) in THF (1.5 mL), MeOH (0.7 mL) and water (0.7 mL) at RT for 1 h. Purified by reverse phase chromatography (32 g C18, 20-50% MeCN in 0.1% aqueous ammonia) then preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 10 min) to provide the title compound (16 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.98 (s, 1H), 7.07 (d, 1H), 6.88 (s, 2H), 6.69 (d, 1H), 6.63 (dd, 1H), 5.96 – 5.86 (m, 1H), 5.54 – 5.46 (m, 1H), 3.99 – 3.86 (m, 2H), 3.39 – 3.17 (m, 4H), 3.13 – 2.85 (m, 3H), 2.60 – 2.42 (m, 2H), 2.30 (s, 3H), 2.10 – 1.82 (m, 8H), 1.79 – 0.69 (m, 10H). LCMS (Method 21): 3.61 min, 704.1 $[M+H]^+$.

**Example 53:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



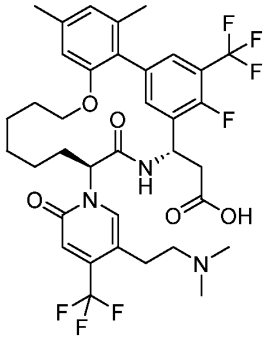
**[001413]** Prepared in an analogous manner to **Example 27** using **Intermediate 335** (44 mg, 59 µmol) and lithium hydroxide (2.1 mg, 88 µmol) in THF (0.8 mL), MeOH (0.4 mL) and water (0.4 mL) at RT for 1 h. Purified by reverse phase chromatography (32 g C18, 20-50% MeCN in 0.1% aqueous ammonia) then preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 10 min) to provide the title compound (18 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.69 (s, 1H), 7.09 (d, 1H), 6.91 – 6.85 (m, 1H), 6.74 – 6.67 (m, 2H), 6.40 (s, 1H), 5.96 – 5.90 (m, 1H), 5.50 – 5.44 (m, 1H), 3.97 – 3.88 (m, 2H), 3.19 – 2.97 (m, 2H), 2.92 – 2.77 (m, 2H), 2.73 (s, 6H), 2.64 – 2.41 (m, 2H), 2.31 (s, 3H), 2.28 (s, 3H), 2.24 (s, 3H), 2.20 – 2.03 (m, 1H), 1.98 (s, 3H), 1.59 – 1.06 (m, 9H). LCMS (Method 21): 3.20 min, 620.3 $[M+H]^+$.

**Example 54:** 2-((10*S*,13*S*)-2$^4$-Cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001414]** Prepared in an analogous manner to **Example 27** using **Intermediate 345** (32 mg, 44 μmol) and lithium hydroxide (4.2 mg, 0.18 mmol) in THF (0.5 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 2 h. Purified by reverse phase chromatography (32 g C18, 10-60% MeCN in 0.1% aqueous ammonia) then preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 10 min) to provide the title compound (6.4 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.99 (s, 1H), 7.09 (d, 1H), 6.92 – 6.84 (m, 2H), 6.65 – 6.59 (m, 2H), 5.99 – 5.89 (m, 1H), 5.50 – 5.44 (m, 1H), 3.98 – 3.80 (m, 2H), 3.19 – 3.07 (m, 1H), 3.00 – 2.91 (m, 2H), 2.74 (s, 6H), 2.66 – 2.45 (m, 2H), 2.30 (s, 3H), 2.16 – 2.05 (m, 1H), 1.99 (s, 3H), 1.94 – 1.84 (m, 1H), 1.67 – 1.17 (m, 10H), 0.99 – 0.93 (m, 2H), 0.73 – 0.67 (m, 2H). LCMS (Method 19): 3.25 min, 700.5 $[M+H]^+$.

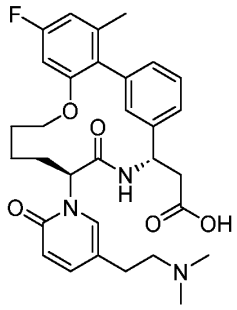
**Example 55:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001415]** Prepared in an analogous manner to **Example 27** using **Intermediate 354** (78 mg, 75 μmol) and lithium hydroxide (2.7 mg, 0.11 mmol) in THF (0.9 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by reverse phase chromatography (32 g C18, 20-50% MeCN in 0.1% aqueous ammonia) then preparative HPLC (XBridge C18 30 x 250 mm 5 μm,

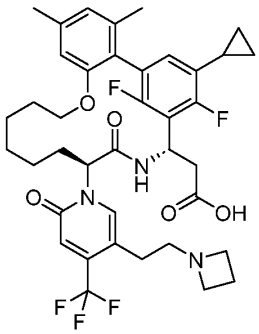
eluting 35-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (46 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.95 (s, 1H), 7.56 (d, 1H), 7.37 – 7.29 (m, 1H), 6.87 (s, 1H), 6.79 – 6.70 (m, 2H), 5.99 – 5.94 (m, 1H), 5.50 – 5.44 (m, 1H), 3.99 – 3.80 (m, 2H), 3.19 – 3.07 (m, 1H), 2.97 – 2.90 (m, 2H), 2.74 – 2.50 (m, 7H), 2.33 (s, 3H), 2.09 – 1.99 (m, 5H), 1.61 – 1.03 (m, 10H). LCMS (Method 21): 3.10 min, 728.2 $[M+H]^+$.

**Example 56:** 2-((8*S*,11*S*)-8-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-2$^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid



**[001416]** Prepared in an analogous manner to **Example 27** using **Intermediate 361** (24 mg, 43 μmol) and lithium hydroxide (3.1 mg, 0.13 mmol) in THF (0.9 mL), MeOH (0.6 mL) and water (0.6 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 20-40% MeCN in 0.1% aqueous ammonia over 30 min) to provide the title compound (2.5 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.84 (d, 1H), 7.44 (dd, 1H), 7.41 – 7.25 (m, 3H), 7.00 – 6.94 (m, 1H), 6.58 (d, 2H), 6.49 (d, 1H), 5.52 – 5.47 (m, 1H), 5.22 – 5.17 (m, 1H), 4.08 – 4.01 (m, 1H), 3.78 – 3.71 (m, 1H), 2.67 – 2.60 (m, 6H), 2.40 (s, 6H), 2.06 (s, 3H), 1.72 – 1.52 (m, 4H), 1.40 – 1.29 (m, 2H). LCMS (Method 19): 2.50 min, 550.1 $[M+H]^+$.

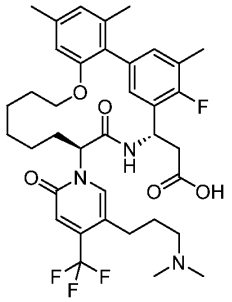
**Example 57:** 2-((10*S*,13*S*)-10-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^5$-cyclopropyl-1$^2$,1$^4$-difluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001417]** Prepared in an analogous manner to **Intermediate 8** using **Intermediate 367** (0.15 g, 0.21 mmol) and 10% palladium on carbon (22 mg) in ethanol (21 mL) and MeOH (4

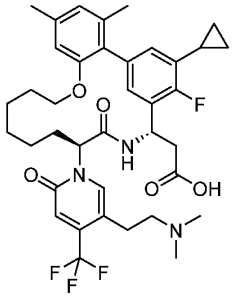
mL) under a hydrogen atmosphere at RT for 4 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-50% MeCN in 0.1% aqueous ammonia over 30 min) to provide the title compound (10 mg). to provide the title compound (52 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.98 (s, 1H), 6.86 (s, 1H), 6.73 (s, 2H), 6.61 (dd, 1H), 6.06 – 6.01 (m, 1H), 5.53 – 5.49 (m, 1H), 4.04 – 3.96 (m, 4H), 3.93 – 3.87 (m, 2H), 2.91 – 2.83 (m, 2H), 2.80 – 2.70 (m, 2H), 2.64 – 2.58 (m, 1H), 2.48 – 2.38 (m, 2H), 2.32 (s, 3H), 2.11 – 2.02 (m, 2H), 1.96 (s, 3H), 1.65 – 1.15 (m, 10H), 0.99 – 0.93 (m, 2H), 0.69 – 0.62 (m, 2H). LCMS (Method 21): 3.34 min, 730.3 $[M+H]^+$.

**Example 58:** 2-((10*S*,13*S*)-10-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



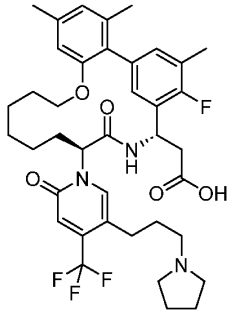
**[001418]** Prepared in an analogous manner to **Example 27** using **Intermediate 371** (23 mg, 32 µmol) and lithium hydroxide (5 mg, 0.12 mmol) in THF (0.5 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 2.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 30 min) to provide the title compound (10 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.97 (s, 1H), 7.06 (dd, 1H), 6.88 (d, 1H), 6.83 (s, 1H), 6.76 – 6.69 (m, 2H), 5.90 (d, 1H), 5.46 (d, 1H), 3.93 – 3.86 (m, 2H), 2.91 – 2.81 (m, 2H), 2.75 (s, 6H), 2.65 – 2.43 (m, 4H), 2.33 – 2.27 (m, 6H), 2.20 – 1.99 (m, 3H), 1.95 (s, 3H), 1.54 – 1.24 (m, 9H). LCMS (Method 21): 2.75 min, 688.3 $[M+H]^+$.

**Example 59:** 2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



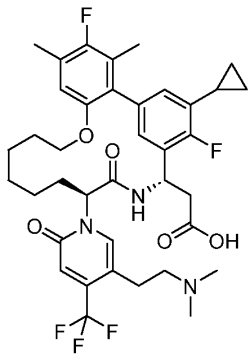
**[001419]** Prepared in an analogous manner to **Example 27** using **Intermediate 385** (0.14 g, 0.12 mmol) and lithium hydroxide (8.4 mg, 0.35 mmol) in THF (2.5 mL), MeOH (1.5 mL) and water (1.5 mL) at RT for 1.5 h. Purified by reverse phase chromatography (20 g C18, 0-60% MeCN in 0.1% aqueous ammonia) then preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (36 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.15 (s, 1H), 7.07 (d, 1H), 6.85 (s, 1H), 6.74 – 6.65 (m, 2H), 6.62 – 6.52 (m, 1H), 6.08 – 5.93 (m, 1H), 5.58 – 5.32 (m, 1H), 3.99 – 3.78 (m, 2H), 3.15 – 2.84 (m, 4H), 2.70 (s, 6H), 2.66 – 2.52 (m, 2H), 2.30 (s, 3H), 2.20 – 2.05 (m, 2H), 1.94 (s, 3H), 1.70 – 1.10 (m, 9H), 0.99 – 0.92 (m, 2H), 0.71 – 0.63 (m, 2H). LCMS (Method 15): 1.35 min, 700.2 $[M+H]^+$.

**Example 60:** 2-((10*S*,13*S*)-1$^4$-Fluoro-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-10-(2-oxo-5-(3-(pyrrolidin-1-yl)propyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



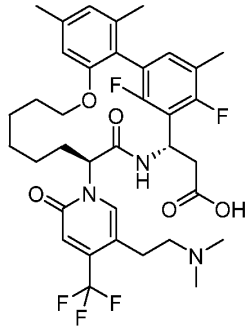
**[001420]** Prepared in an analogous manner to **Example 27** using **Intermediate 387** (44 mg, 59 µmol) and lithium hydroxide monohydrate (10 mg, 0.24 mmol) in THF (0.5 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (10 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.98 (s, 1H), 7.08 (dd, 1H), 6.89 (d, 1H), 6.83 (s, 1H), 6.77 – 6.69 (m, 2H), 6.07 – 5.92 (m, 1H), 5.51 – 5.41 (m, 1H), 3.99 – 3.82 (m, 2H), 3.24 – 3.09 (m, 4H), 3.03 – 2.90 (m, 2H), 2.74 – 2.46 (m, 4H), 2.37 – 2.28 (m, 6H), 2.13 – 1.93 (m, 10H), 1.68 – 1.10 (m, 9H). LCMS (Method 21): 3.78 min, 714.3 $[M+H]^+$.

**Example 61:** 2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^5$-difluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001421]** Prepared in an analogous manner to **Example 27** using **Intermediate 396** (0.21 g, 0.19 mmol) and lithium hydroxide (14 mg, 0.58 mmol) in THF (3.6 mL), MeOH (2.2 mL) and water (2.2 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (54 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.04 (s, 1H), 7.08 (d, 1H), 6.85 (s, 1H), 6.78 (d, 1H), 6.57 (d, 1H), 5.98 (dd, 1H), 5.49 (dd, 1H), 3.95 – 3.79 (m, 2H), 3.07 – 2.80 (m, 4H), 2.67 (s, 6H), 2.64 – 2.48 (m, 2H), 2.26 (d, 3H), 2.20 – 2.02 (m, 2H), 1.89 (d, 3H), 1.70 – 1.10 (m, 9H), 1.01 – 0.93 (m, 2H), 0.71 – 0.64 (m, 2H). LCMS (Method 15): 1.54 min, 718.2 $[M+H]^+$.

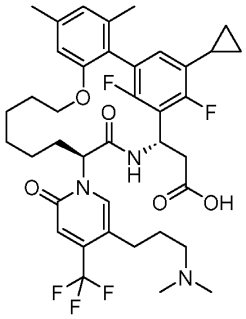
**Example 62:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^2$,1$^4$-difluoro-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001422]** Prepared in an analogous manner to **Example 27** using **Intermediate 409** (73 mg, 30 µmol) and lithium hydroxide (7.3 mg, 0.30 mmol) in THF (1.2 mL), MeOH (0.7 mL) and water (0.7 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (10 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.05 (s, 1H), 6.98 – 6.81 (m, 2H), 6.71 (s,

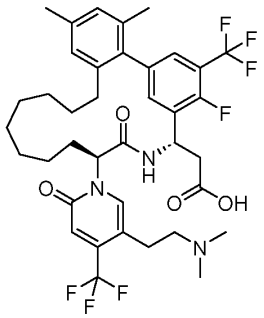
2H), 5.99 – 5.93 (m, 1H), 5.53 (dd, 1H), 3.98 – 3.87 (m, 2H), 3.01 – 2.80 (m, 6H), 2.52 (s, 6H), 2.32 (s, 3H), 2.26 (s, 3H), 2.09 – 1.95 (m, 4H), 1.72 – 0.84 (m, 9H). LCMS (Method 15): 1.34 min, 692.2 $[M+H]^+$.

**Example 63:** 2-((10*S*,13*S*)-$1^5$-Cyclopropyl-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^2$,$1^4$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid

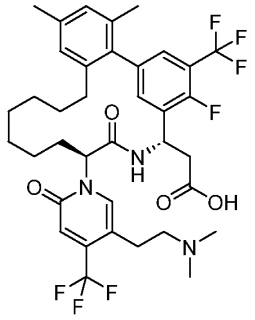


**[001423]** Prepared in an analogous manner to **Example 27** using **Intermediate 413** (0.11 g, 0.14 mmol) and lithium hydroxide (10 mg, 0.43 mmol) in THF (3.1 mL), MeOH (1.8 mL) and water (1.8 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 22 min) to provide the title compound (24 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.02 (s, 1H), 6.82 (s, 1H), 6.72 (s, 1H), 6.71 – 6.57 (m, 2H), 6.03 – 5.93 (m, 1H), 5.54 – 5.36 (m, 1H), 3.93 – 3.59 (m, 2H), 3.03 – 2.59 (m, 6H), 2.57 (s, 6H), 2.32 (s, 3H), 2.10 – 1.83 (m, 6H), 1.68 – 1.12 (m, 8H), 1.07 – 0.88 (m, 4H), 0.67 – 0.58 (m, 2H). LCMS (Method 21): 3.07 min, 732.2 $[M+H]^+$.

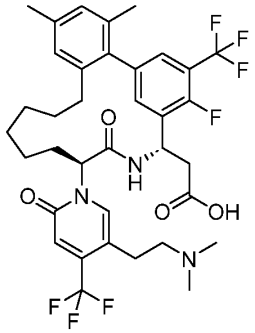
**Example 64:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotetradecaphane-3-yl)acetic acid



**Example 65:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

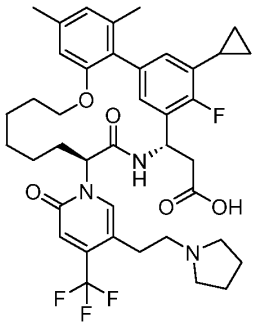


**Example 66:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



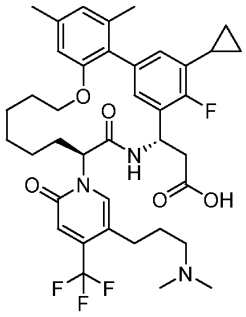
**[001424]** Prepared in an analogous manner to **Example 27** using **Intermediate 420** (0.18 g, 0.23 mmol) and lithium hydroxide (16.5 mg, 0.69 mmol) in THF (5 mL), MeOH (3 mL) and water (3 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 22 min) to provide **Example 64** (6.6 mg), **Example 65** (2.9 mg), and **Example 66** (5.1 mg). **Example 64:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.10 (s, 1H), 7.54 (d, 1H), 7.32 (d, 1H), 6.98 (s, 1H), 6.95 (s, 1H), 6.88 (s, 1H), 6.01 (dd, 1H), 5.49 – 5.35 (m, 1H), 3.09 – 2.80 (m, 6H), 2.73 – 2.51 (m, 6H), 2.49 – 2.07 (m, 5H), 1.97 (s, 3H), 1.66 – 0.43 (m, 14H). LCMS (Method 21): 3.72 min, 740.2 $[M+H]^+$. **Example 65:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.85 (s, 1H), 7.52 (dd, 1H), 7.27 (dd, 1H), 6.97 (s, 1H), 6.94 (s, 1H), 6.88 (s, 1H), 5.99 (dd, 1H), 5.45 (dd, 1H), 3.29 – 3.10 (m, 2H), 3.01 – 2.84 (m, 2H), 2.79 (s, 6H), 2.60 (dd, 1H), 2.41 (dd, 1H), 2.40 – 2.33 (m, 2H), 2.31 (s, 3H), 2.25 – 2.10 (m, 2H), 1.92 (s, 3H), 1.61 – 0.96 (m, 10H). LCMS (Method 21): 3.90 min, 726.2 $[M+H]^+$. **Example 66:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.99 (s, 1H), 7.57 (dd, 1H), 7.30 (dd, 1H), 6.95 (s, 1H), 6.93 (s, 1H), 6.85 (s, 1H), 5.75 (dd, 1H), 5.44 (dd, 1H), 2.80 – 2.45 (m, 6H), 2.38 – 2.25 (m, 10H), 2.04 – 1.86 (m, 4H), 1.71 – 1.56 (m, 1H), 1.52 – 0.96 (m, 9H). LCMS (Method 21): 3.67 min, 712.2 $[M+H]^+$. LCMS (Method 21): 3.67 min, 712.2 $[M+H]^+$.

**Example 67:** 2-((10*S*,13*S*)-1$^5$-Cyclopropyl-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001425]** Prepared in an analogous manner to **Example 27** using **Intermediate 423** (0.13 g, 0.11 mmol) and lithium hydroxide (8.2 mg, 0.34 mmol) in THF (1.3 mL), MeOH (0.8 mL) and water (0.8 mL) at RT for 1.5 h. Purified by reverse phase chromatography (20 g C18, 0-60% MeCN in 0.1% aqueous ammonia) then preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (24 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.11 (s, 1H), 7.06 (d, 1H), 6.87 (s, 1H), 6.76 – 6.69 (m, 2H), 6.56 (d, 1H), 6.02 – 5.89 (m, 1H), 5.57 – 5.44 (m, 1H), 3.99 – 3.78 (m, 2H), 3.31 – 3.10 (m, 5H), 3.05 – 2.90 (m, 2H), 2.65 – 2.44 (m, 2H), 2.32 (s, 3H), 2.22 – 1.96 (m, 7H), 1.96 (s, 3H), 1.67 – 1.11 (m, 9H), 1.06 – 0.89 (m, 2H), 0.76 – 0.61 (m, 2H). LCMS (Method 15): 1.91 min, 726.3 $[M+H]^+$.

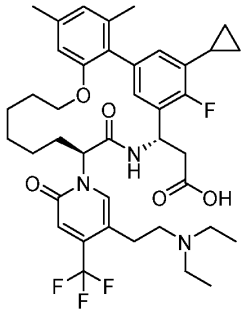
**Example 68:** 2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001426]** Prepared in an analogous manner to **Example 27** using **Intermediate 427** (79 mg, 0.09 mmol) and lithium hydroxide (6.7 mg, 0.28 mmol) in THF (1.0 mL), MeOH (0.3 mL) and water (0.2 mL) at RT for 1 h. Purified by reverse phase chromatography (38 g C18, 40-60% MeCN in 0.1% aqueous ammonia) to provide the title compound (29 mg). $^1$H NMR (400

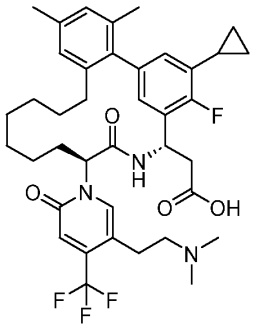
MHz, $CD_3OD$) δ: 8.03 (s, 1H), 7.05 (d, 1H), 6.84 (s, 1H), 6.77 – 6.68 (m, 2H), 6.57 (d, 1H), 6.09 – 5.95 (m, 1H), 5.53 – 5.41 (m, 1H), 3.99 – 3.80 (m, 2H), 3.04 – 2.83 (m, 2H), 2.72 (s, 6H), 2.71 – 2.43 (m, 4H), 2.32 (s, 3H), 2.20 – 1.95 (m, 4H), 1.94 (s, 3H), 1.69 – 1.57 (m, 1H), 1.54 – 1.12 (m, 8H), 1.06 – 0.90 (m, 2H), 0.78 – 0.60 (m, 2H). LCMS (Method 15): 1.76 min, 714.3 $[M+H]^+$.

**Example 69:** 2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid

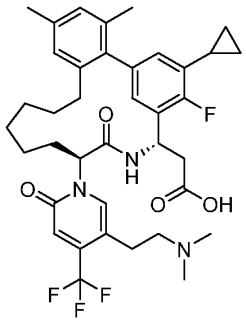


**[001427]** Prepared in an analogous manner to **Example 27** using **Intermediate 431** (0.13 g, 0.17 mmol) and lithium hydroxide (12 mg, 0.51 mmol) in THF (1.0 mL), MeOH (0.2 mL) and water (0.3 mL) at RT for 1 h. Purified by reverse phase chromatography (38 g C18, 40-60% MeCN in 0.1% aqueous ammonia) then preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (36 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.32 (s, 1H), 7.09 (d, 1H), 6.87 (s, 1H), 6.77 – 6.67 (m, 2H), 6.53 (d, 1H), 6.10 – 6.00 (m, 1H), 5.57 – 5.43 (m, 1H), 3.96 (dt, 1H), 3.89 – 3.77 (m, 1H), 3.25 – 2.91 (m, 8H), 2.68 – 2.51 (m, 2H), 2.32 (s, 3H), 2.16 – 1.99 (m, 2H), 1.94 (s, 3H), 1.71 – 1.58 (m, 1H), 1.55 – 1.05 (m, 14H), 1.02 – 0.91 (m, 2H), 0.74 – 0.60 (m, 2H). LCMS (Method 15): 1.80 min, 728.3 $[M+H]^+$.

**Example 70:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

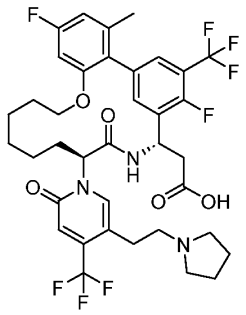


**Example 71:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



**[001428]** Prepared in an analogous manner to **Example 27** using **Intermediate 439** (0.13 g, 0.11 mmol) and lithium hydroxide (7.5 mg, 0.32 mmol) in THF (2.2 mL), MeOH (1.3 mL) and water (1.3 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 70** (36 mg), and **Example 71** (19 mg). **Example 70:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.90 (s, 1H), 7.04 (d, 1H), 6.91 (s, 1H), 6.90 – 6.82 (m, 2H), 6.52 (d, 1H), 5.93 (dd, 1H), 5.50 – 5.42 (m, 1H), 3.09 – 2.76 (m, 4H), 2.62 (s, 6H), 2.53 – 2.39 (m, 2H), 2.35 – 2.11 (m, 6H), 1.91 (s, 3H), 1.62 – 0.90 (m, 14H), 0.76 – 0.61 (m, 2H). LCMS (Method 15): 2.00 min, 698.3 $[M+H]^+$. **Example 71:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.03 (s, 1H), 7.07 (dd, 1H), 6.90 (s, 1H), 6.86 (s, 1H), 6.81 (s, 1H), 6.54 (dd, 1H), 5.78 (dd, 1H), 5.45 (dd, 1H), 2.83 – 2.74 (m, 2H), 2.71 – 2.50 (m, 5H), 2.40 (s, 6H), 2.29 (s, 3H), 2.28 – 2.11 (m, 2H), 2.01 – 1.88 (m, 4H), 1.67 – 1.56 (m, 1H), 1.53 – 0.88 (m, 10H), 0.79 – 0.61 (m, 2H). LCMS (Method 15): 1.91 min, 684.3 $[M+H]^+$.

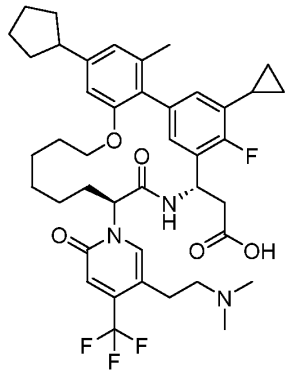
**Example 72:** 2-((10*S*,13*S*)-1$^4$,2$^4$-Difluoro-2$^6$-methyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001429]** Prepared in an analogous manner to **Example 27** using **Intermediate 450** (52 mg, 33 µmol) and lithium hydroxide (1.2 mg, 49 µmol) in THF (1.0 mL), MeOH (0.5 mL) and water (0.3 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm,

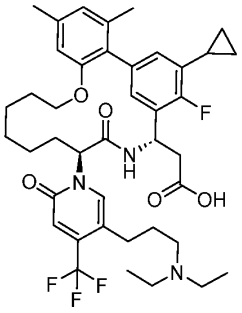
eluting 30-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (14 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.00 (s, 1H), 7.57 (d, 1H), 7.34 (d, 1H), 6.88 (s, 1H), 6.75 (d, 1H), 6.68 (dd, 1H), 6.00 – 5.88 (m, 1H), 5.57 – 5.44 (m, 1H), 4.08 – 3.87 (m, 2H), 3.31 – 3.10 (m, 5H), 3.03 – 2.87 (m, 2H), 2.72 – 2.51 (m, 2H), 2.22 – 1.91 (m, 8H), 1.67 – 1.48 (m, 3H), 1.47 – 1.11 (m, 7H). LCMS (Method 15): 1.88 min, 758.3 $[M+H]^+$.

**Example 73:** 2-((10*S*,13*S*)-2$^4$-Cyclopentyl-1$^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



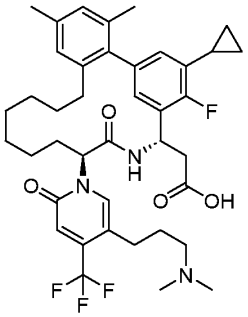
**[001430]** Prepared in an analogous manner to **Example 27** using **Intermediate 464** (90 mg, 0.12 mmol) and lithium hydroxide (8.3 mg, 0.35 mmol) in THF (2.8 mL), MeOH (1.4 mL) and water (1.4 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (27 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.04 (s, 1H), 7.09 (d, 1H), 6.84 (s, 1H), 6.74 (s, 2H), 6.57 (d, 1H), 6.01 – 5.86 (m, 1H), 5.57 – 5.29 (m, 1H), 4.03 – 3.77 (m, 2H), 3.06 – 2.76 (m, 5H), 2.70 – 2.40 (m, 8H), 2.19 – 2.01 (m, 4H), 1.97 (s, 3H), 1.90 – 1.81 (m, 2H), 1.78 – 1.36 (m, 7H), 1.35 – 1.11 (m, 5H), 1.05 – 0.86 (m, 3H), 0.76 – 0.61 (m, 2H). LCMS (Method 21): 3.96 min, 754.3 $[M+H]^+$.

**Example 74:** 2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(3-(diethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



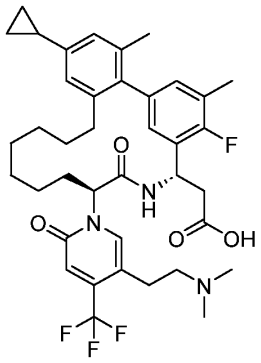
**[001431]** Prepared in an analogous manner to **Example 27** using **Intermediate 466** (14 mg, 18 μmol) and lithium hydroxide (0.65 mg, 27 μmol) in THF (0.5 mL), MeOH (0.3 mL) and water (0.1 mL) at RT for 14 h. Purified by reverse phase chromatography (20 g C18, 40-60% MeCN in 0.1% aqueous ammonia) to provide the title compound (6 mg). $^1$H NMR (500 MHz, $CD_3OD$) δ: 7.96 (s, 1H), 7.05 (d, 1H), 6.83 (s, 1H), 6.75 – 6.68 (m, 2H), 6.57 (d, 1H), 6.03 – 5.94 (m, 1H), 5.51 – 5.42 (m, 1H), 3.95 – 3.82 (m, 2H), 3.24 – 2.86 (m, 7H), 2.70 – 2.62 (m, 2H), 2.61 – 2.48 (m, 2H), 2.32 (s, 3H), 2.17 – 2.04 (m, 2H), 2.02 – 1.89 (m, 4H), 1.67 – 1.58 (m, 1H), 1.55 – 1.50 (m, 2H), 1.43 – 1.33 (m, 2H), 1.30 – 1.15 (m, 10H), 1.02 – 0.95 (m, 2H), 0.73 – 0.64 (m, 2H). LCMS (Method 11): 1.78 min, 740.6 $[M-H]^-$.

**Example 75:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

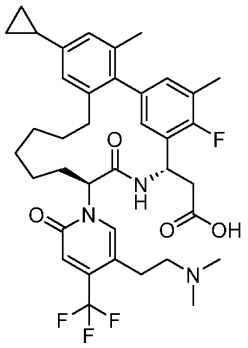


**[001432]** Prepared in an analogous manner to **Example 27** using **Intermediate 470** (24 mg, 32 μmol) and lithium hydroxide (1.2 mg, 49 μmol) in THF (1.0 mL), MeOH (1.0 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 30-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (4 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.89 (s, 1H), 7.02 (dd, 1H), 6.92 (s, 1H), 6.89 (s, 1H), 6.84 (s, 1H), 6.53 (dd, 1H), 6.06 – 5.97 (m, 1H), 5.42 (dd, 1H), 2.96 – 2.68 (m, 4H), 2.67 (s, 6H), 2.65 – 2.37 (m, 3H), 2.30 (s, 3H), 2.29 – 2.11 (m, 3H), 1.90 (s, 3H), 1.61 – 0.84 (m, 15H), 0.76 – 0.64 (m, 2H). LCMS (Method 21): 4.42 min, 712.3 $[M+H]^+$.

**Example 76:** 2-((3*S*,6*S*)-1$^4$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

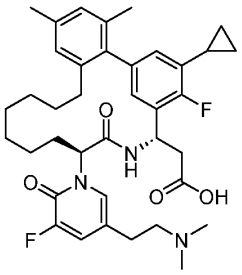


**Example 77:** 2-((3*S*,6*S*)-1$^4$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



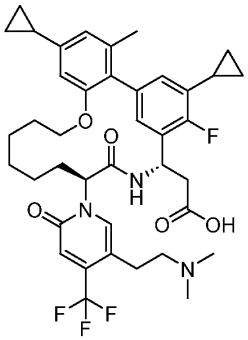
**[001433]** Prepared in an analogous manner to **Example 27** using **Intermediate 478** (0.25 g, 0.27 mmol) and lithium hydroxide (19 mg, 0.81 mmol) in THF (7 mL), MeOH (4 mL) and water (4 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 76** (54 mg), and **Example 77** (9 mg). **Example 76:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.92 (s, 1H), 7.09 (d, 1H), 6.86 – 6.72 (m, 4H), 5.86 (dd, 1H), 5.48 (dd, 1H), 2.92 – 2.67 (m, 4H), 2.60 (dd, 1H), 2.53 – 2.33 (m, 9H), 2.31 (s, 3H), 2.24 – 2.12 (m, 1H), 1.93 (s, 3H), 1.90 – 1.81 (m, 1H), 1.60 – 0.99 (m, 11H), 0.97 – 0.87 (m, 2H), 0.74 – 0.60 (m, 2H). LCMS (Method 11): 1.76 min, 698.7 $[M+H]^+$. **Example 77:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.01 (s, 1H), 7.11 (dd, 1H), 6.85 (dd, 1H), 6.80 (s, 1H), 6.77 (s, 1H), 6.76 (s, 1H), 5.74 (dd, 1H), 5.45 (dd, 1H), 2.75 (t, 2H), 2.66 – 2.46 (m, 5H), 2.33 (s, 6H), 2.31 (s, 3H), 2.30 – 2.12 (m, 1H), 1.94 (s, 3H), 1.93 – 1.77 (m, 2H), 1.68 – 1.55 (m, 1H), 1.54 – 1.02 (m, 8H), 0.99 – 0.86 (m, 2H), 0.72 – 0.62 (m, 2H). LCMS (Method 11): 1.73 min, 684.2 $[M+H]^+$.

**Example 78:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

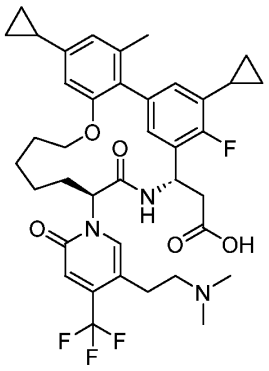


**[001434]** Prepared in an analogous manner to **Example 27** using **Intermediate 481** (0.14 g, 0.13 mmol) and lithium hydroxide (4.5 mg, 0.19 mmol) in THF (1.5 mL), MeOH (0.6 mL) and water (0.3 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (68 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.52 (s, 1H), 7.37 (dd, 1H), 7.03 (dd, 1H), 6.91 (s, 1H), 6.88 (s, 1H), 6.52 (dd, 1H), 5.87 (dd, 1H), 5.53 (dd, 1H), 3.14 – 2.95 (m, 2H), 2.92 – 2.68 (m, 3H), 2.64 (s, 6H), 2.63 – 2.55 (m, 1H), 2.50 – 2.35 (m, 1H), 2.30 (s, 3H), 2.29 – 2.10 (m, 3H), 1.90 (s, 3H), 1.59 – 1.45 (m, 2H), 1.44 – 1.03 (m, 9H), 1.02 – 0.96 (m, 2H), 0.74 – 0.65 (m, 2H). LCMS (Method 21): 3.95 min, 648.2 $[M+H]^+$.

**Example 79:** 2-((10*S*,13*S*)-1$^5$,2$^4$-Dicyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid

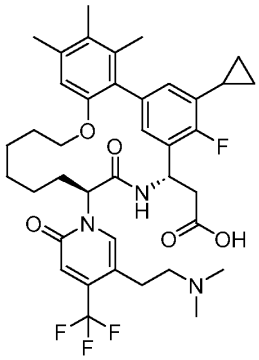


**Example 80:** 2-((9*S*,12*S*)-1$^5$,2$^4$-Dicyclopropyl-9-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-10-oxo-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid

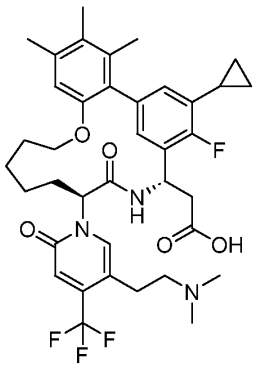


**[001435]** Prepared in an analogous manner to **Example 27** using **Intermediate 494** (76 mg, 0.10 mmol) and lithium hydroxide (7.3 mg, 0.30 mmol) in THF (2.4 mL), MeOH (1.2 mL) and water (1.2 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 79** (36 mg), and **Example 80** (6.3 mg). **Example 79:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.03 (s, 1H), 7.09 (d, 1H), 6.83 (s, 1H), 6.64 – 6.49 (m, 3H), 5.96 – 5.86 (m, 1H), 5.56 – 5.39 (m, 1H), 4.02 – 3.78 (m, 2H), 2.90 – 2.56 (m, 6H), 2.47 (s, 6H), 2.20 – 1.97 (m, 2H), 1.95 (s, 3H), 1.93 – 1.82 (m, 1H), 1.68 – 1.08 (m, 9H), 1.02 – 0.87 (m, 4H), 0.75 – 0.61 (m, 4H). LCMS (Method 21): 3.85 min, 726.3 $[M+H]^+$. **Example 80:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.03 (s, 1H), 7.05 (dd, 1H), 6.83 (s, 1H), 6.56 – 6.47 (m, 3H), 5.73 (dd, 1H), 5.56 (dd, 1H), 4.07 – 3.96 (m, 1H), 3.88 – 3.80 (m, 1H), 2.79 – 2.69 (m, 2H), 2.64 – 2.45 (m, 4H), 2.33 (s, 6H), 2.19 – 2.02 (m, 2H), 1.94 (s, 3H), 1.93 – 1.84 (m, 1H), 1.82 – 1.71 (m, 1H), 1.68 – 1.27 (m, 6H), 1.03 – 0.88 (m, 4H), 0.73 – 0.62 (m, 4H). LCMS (Method 21): 3.62 min, 712.3 $[M+H]^+$.

**Example 81:** 2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^5$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid

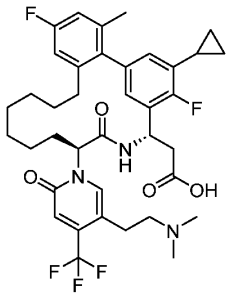


**Example 82:** 2-((9*S*,12*S*)-1$^5$-Cyclopropyl-9-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^5$,2$^6$-trimethyl-10-oxo-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid

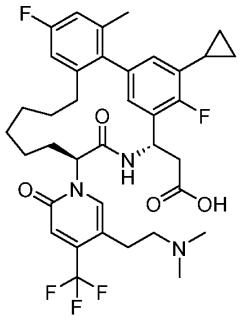


**[001436]** Prepared in an analogous manner to **Example 27** using **Intermediate 502** (0.12 g, 0.11 mmol) and lithium hydroxide (7.6 mg, 0.32 mmol) in THF (1.6 mL), MeOH (0.6 mL) and water (0.3 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 81** (27 mg), and **Example 82** (5.4 mg). **Example 81:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.09 (s, 1H), 7.07 (dd, 1H), 6.85 (s, 1H), 6.74 (s, 1H), 6.53 (dd, 1H), 5.98 (dd, 1H), 5.50 (dd, 1H), 3.96 – 3.87 (m, 1H), 3.85 – 3.77 (m, 1H), 3.08 – 2.69 (m, 3H), 2.68 – 2.45 (m, 8H), 2.31 (s, 3H), 2.16 (s, 3H), 2.15 – 2.03 (m, 2H), 1.91 (s, 3H), 1.67 – 1.56 (m, 1H), 1.55 – 1.07 (m, 8H), 1.06 – 0.78 (m, 3H), 0.75 – 0.58 (m, 2H). LCMS (Method 11): 1.74 min, 714.3 $[M+H]^+$. **Example 82:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.04 (s, 1H), 7.07 (dd, 1H), 6.86 (s, 1H), 6.64 (s, 1H), 6.51 (dd, 1H), 5.79 (dd, 1H), 5.56 (dd, 1H), 4.05 – 3.95 (m, 1H), 3.90 – 3.77 (m, 1H), 2.83 – 2.61 (m, 3H), 2.61 (dd, 1H), 2.51 (dd, 1H), 2.42 (s, 6H), 2.33 (s, 3H), 2.17 (s, 3H), 2.17 – 2.00 (m, 2H), 1.93 (s, 3H), 1.84 – 1.73 (m, 1H), 1.72 – 1.62 (m, 1H), 1.61 – 1.14 (m, 6H), 1.07 – 0.86 (m, 2H), 0.79 – 0.64 (m, 2H). LCMS (Method 15): 1.72 min, 700.3 $[M+H]^+$.

**Example 83:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^6$,2$^4$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

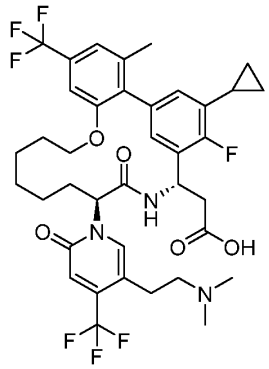


**Example 84:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid

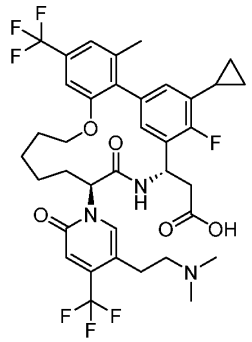


**[001437]** Prepared in an analogous manner to **Example 27** using **Intermediate 511** (0.17 g, 0.19 mmol) and lithium hydroxide (14 mg, 0.57 mmol) in THF (5 mL), MeOH (2.5 mL) and water (1.0 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 83** (36 mg), and **Example 84** (6.3 mg). **Example 83:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.90 (s, 1H), 7.05 (dd, 1H), 6.89 – 6.77 (m, 3H), 6.54 (dd, 1H), 5.92 (dd, 1H), 5.47 (dd, 1H), 3.06 – 2.75 (m, 4H), 2.69 – 2.51 (m, 7H), 2.45 (dd, 1H), 2.39 – 2.27 (m, 2H), 2.26 – 2.09 (m, 2H), 1.95 (s, 3H), 1.61 – 1.03 (m, 11H), 1.03 – 0.96 (m, 2H), 0.77 – 0.61 (m, 2H). LCMS (Method 15): 1.78 min, 702.2 $[M+H]^+$. **Example 84:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.00 (s, 1H), 7.09 (dd, 1H), 6.87 – 6.75 (m, 3H), 6.55 (dd, 1H), 5.76 (dd, 1H), 5.45 (dd, 1H), 2.83 – 2.72 (m, 2H), 2.71 – 2.48 (m, 5H), 2.35 (s, 6H), 2.34 – 2.24 (m, 1H), 2.22 – 2.11 (m, 1H), 2.07 – 1.89 (m, 4H), 1.80 – 1.56 (m, 1H), 1.54 – 1.05 (m, 8H), 1.04 – 0.85 (m, 2H), 0.77 – 0.61 (m, 2H). LCMS (Method 21): 1.70 min, 688.2 $[M+H]^+$.

**Example 85:** 2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-11-oxo-2$^4$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid

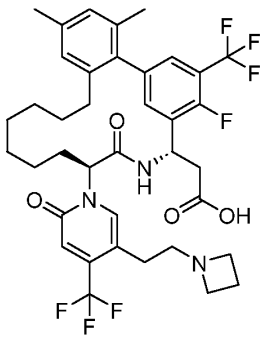


**Example 86:** 2-((9*S*,12*S*)-1$^5$-Cyclopropyl-9-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-10-oxo-2$^4$-(trifluoromethyl)-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid



**[001438]** Prepared in an analogous manner to **Example 27** using **Intermediate 519** (86 mg, 65 µmol) and lithium hydroxide (6 mg, 0.25 mmol) in THF (0.5 mL), MeOH (0.5 mL) and water (0.3 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 22 min) to provide **Example 85** (23 mg), and **Example 86** (5 mg). **Example 85:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.07 (s, 1H), 7.19 (s, 1H), 7.16 (s, 1H), 7.11 (d, 1H), 6.86 (s, 1H), 6.61 (d, 1H), 6.00 (dd, 1H), 5.51 (dd, 1H), 4.12 – 3.88 (m, 2H), 3.20 – 2.81 (m, 3H), 2.71 (s, 6H), 2.65 – 2.48 (m, 3H), 2.24 – 2.08 (m, 2H), 2.07 (s, 3H), 1.70 – 1.48 (m, 3H), 1.45 – 1.11 (m, 6H), 1.06 – 0.94 (m, 2H), 0.80 – 0.62 (m, 2H). LCMS (Method 15): 1.83 min, 754.3 $[M+H]^+$. **Example 86:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.01 (s, 1H), 7.16 (s, 1H), 7.08 (s, 1H), 7.04 (s, 1H), 6.88 (s, 1H), 6.61 (d, 1H), 5.95 – 5.68 (m, 1H), 5.61 – 5.41 (m, 1H), 4.11 – 3.88 (m, 2H), 3.08 – 2.31 (m, 11H), 2.21 – 1.97 (m, 5H), 1.83 – 1.70 (m, 2H), 1.67 – 1.16 (m, 6H), 1.07 – 0.82 (m, 2H), 0.79 – 0.62 (m, 2H). LCMS (Method 15): 1.77 min, 740.3 $[M+H]^+$.

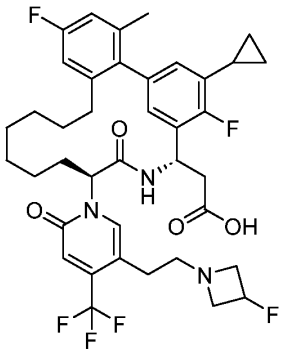
**Example 87:** 2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



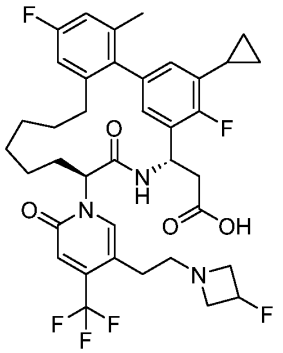
**[001439]** Prepared in an analogous manner to **Example 27** using **Intermediate 528** (79 mg, 0.10 mmol) and lithium hydroxide (3.7 mg, 0.16 mmol) in THF (1.0 mL) and water (0.5 mL) at RT for 1 h. Purified by reverse phase chromatography (32 g C18, 30-70% MeCN in 0.1% aqueous ammonia) to provide the title compound (36 mg). $^1$H NMR (400 MHz, $CD_3OD$)

δ: 7.78 (s, 1H), 7.54 (dd, 1H), 7.30 (dd, 1H), 6.99 (s, 1H), 6.95 (s, 1H), 6.89 (s, 1H), 6.04 (dd, 1H), 5.52 (dd, 1H), 4.21 – 3.96 (m, 4H), 3.46 – 3.33 (m, 2H), 3.01 – 2.88 (m, 1H), 2.82 – 2.69 (m, 1H), 2.67 – 2.59 (m, 1H), 2.54 – 2.34 (m, 4H), 2.33 (s, 3H), 2.30 – 2.20 (m, 1H), 2.18 – 2.06 (m, 1H), 1.93 (s, 3H), 1.61 – 0.85 (m, 11H). LCMS (Method 15): 2.11 min, 738.2 $[M+H]^+$.

**Example 88:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



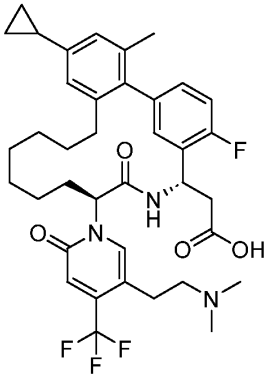
**Example 89:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



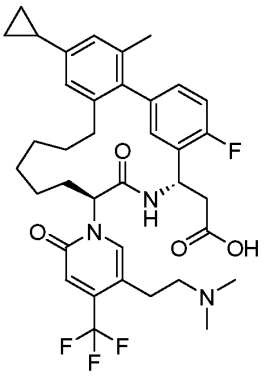
**[001440]** Prepared in an analogous manner to **Example 27** using **Intermediate 534** (0.16 g, 0.20 mmol) and lithium hydroxide (15 mg, 0.61 mmol) in THF (2.5 mL), MeOH (1.3 mL) and water (1.3 mL) at RT for 3 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 88** (52 mg), and **Example 89** (20 mg). **Example 88:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.88 (s, 1H), 7.06 (dd, 1H), 6.87 – 6.78 (m, 3H), 6.54 (dd, 1H), 5.91 (dd, 1H), 5.50 (dd, 1H), 5.40 – 5.07 (m, 1H), 4.10 – 3.95 (m, 2H), 3.75 – 3.56 (m, 2H), 3.09 – 2.96 (m, 2H), 2.83 – 2.58 (m, 3H), 2.49 (dd, 1H), 2.40 – 2.11 (m, 4H), 1.96 (s, 3H), 1.67 – 0.93 (m, 13H), 0.79 – 0.61 (m, 2H). LCMS (Method 21): 3.70 min, 732.2 $[M+H]^+$. **Example 89:** $^1$H NMR (400 MHz, $CD_3OD$)

δ: 8.00 (s, 1H), 7.09 (dd, 1H), 6.85 – 6.77 (m, 3H), 6.56 (dd, 1H), 5.76 (dd, 1H), 5.45 (dd, 1H), 5.28 – 5.02 (m, 1H), 3.80 – 3.67 (m, 2H), 3.43 – 3.32 (m, 2H), 2.83 – 2.71 (m, 2H), 2.69 – 2.51 (m, 5H), 2.38 – 2.28 (m, 1H), 2.22 – 2.12 (m, 1H), 2.07 – 1.90 (m, 4H), 1.70 – 1.44 (m, 1H), 1.42 – 1.05 (m, 8H), 1.04 – 0.96 (m, 2H), 0.78 – 0.61 (m, 2H). LCMS (Method 21): 3.56 min, 718.2 $[M+H]^+$.

**Example 90:** 2-((3*S*,6*S*)-1$^4$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



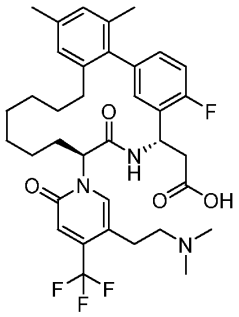
**Example 91:** 2-((3*S*,6*S*)-1$^4$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



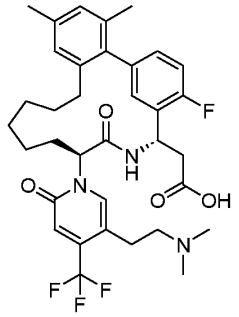
**[001441]** Prepared in an analogous manner to **Example 27** using **Intermediate 543** (0.24 g, 0.18 mmol) and lithium hydroxide (13 mg, 0.55 mmol) in THF (7 mL), MeOH (4 mL) and water (4 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 90** (35 mg), and **Example 91** (17 mg). **Example 90:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.89 (s, 1H), 7.26 (dd, 1H), 7.13 (dd, 1H), 7.10 – 6.94 (m, 1H), 6.87 (s, 1H), 6.83 (d, 1H), 6.77 (d, 1H), 5.93 (dd, 1H), 5.57 (dd, 1H), 3.12 – 2.77 (m, 4H), 2.64 (s, 6H), 2.60 (dd, 1H), 2.45 (dd, 1H), 2.31 (t,

2H), 2.25 – 2.14 (m, 1H), 1.92 (s, 3H), 1.91 – 1.82 (m, 1H), 1.66 – 0.99 (m, 11H), 0.98 – 0.86 (m, 2H), 0.75 – 0.61 (m, 2H). LCMS (Method 15): 1.91 min, 684.3 $[M+H]^+$. **Example 91:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.02 (s, 1H), 7.30 (dd, 1H), 7.11 (dd, 1H), 7.03 – 6.96 (m, 1H), 6.81 (s, 1H), 6.79 (s, 1H), 6.77 (s, 1H), 5.76 (dd, 1H), 5.45 (dd, 1H), 2.85 – 2.51 (m, 7H), 2.40 (s, 6H), 2.35 – 2.15 (m, 1H), 1.95 (s, 3H), 1.94 – 1.82 (m, 2H), 1.69 – 1.55 (m, 1H), 1.54 – 1.01 (m, 8H), 0.99 – 0.86 (m, 2H), 0.78 – 0.59 (m, 2H). LCMS (Method 15): 1.76 min, 670.3 $[M+H]^+$.

**Example 92:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



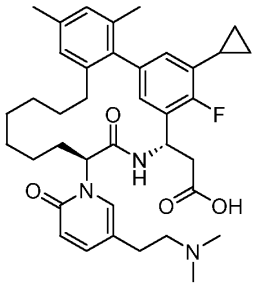
**Example 93:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



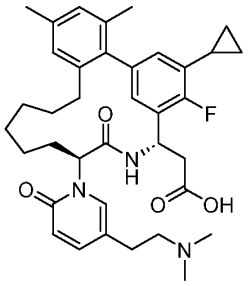
**[001442]** Prepared in an analogous manner to **Example 27** using **Intermediate 552** (0.27 g, 0.40 mmol) and lithium hydroxide (29 mg, 1.19 mmol) in THF (9.5 mL), MeOH (4.8 mL) and water (4.8 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 92** (59 mg), and **Example 93** (22 mg). **Example 92:** $^1$H NMR (500 MHz, $CD_3OD$) δ: 7.89 (s, 1H), 7.27 (dd, 1H), 7.14 (dd, 1H), 7.00 – 6.95 (m, 1H), 6.93 (s, 1H), 6.90 (s, 1H), 6.86 (s, 1H), 5.93 (dd, 1H), 5.47 (dd, 1H), 3.13 – 2.76 (m, 4H), 2.64 (s, 6H), 2.60 (dd, 1H), 2.45 (dd, 1H), 2.38 – 2.25 (m, 5H), 2.24 – 2.14 (m, 1H), 1.93 (s, 3H), 1.65 – 0.86 (m, 11H). LCMS (Method

21): 3.59 min, 658.2 $[M+H]^+$. **Example 93:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.06 (s, 1H), 7.31 (dd, 1H), 7.11 (dd, 1H), 7.04 – 6.97 (m, 1H), 6.92 (s, 1H), 6.88 (s, 1H), 6.82 (s, 1H), 5.79 (dd, 1H), 5.44 (dd, 1H), 3.01 – 2.50 (m, 7H), 2.45 (s, 6H), 2.35 – 2.22 (m, 4H), 2.02 – 1.84 (m, 4H), 1.70 – 1.42 (m, 1H), 1.37 – 0.70 (m, 8H). LCMS (Method 21): 3.28 min, 644.3 $[M+H]^+$.

**Example 94:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



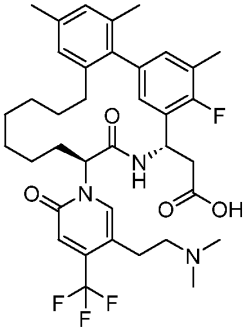
**Example 95:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



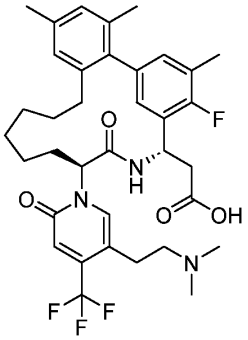
**[001443]** Prepared in an analogous manner to **Example 27** using **Intermediate 555** (99 mg, 0.15 mmol) and lithium hydroxide (11 mg, 0.45 mmol) in THF (1.3 mL), MeOH (0.5 mL) and water (0.3 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 94** (38 mg), and **Example 95** (1.5 mg). **Example 94:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.66 (d, 1H), 7.49 (dd, 1H), 7.00 (dd, 1H), 6.91 (s, 1H), 6.88 (s, 1H), 6.57 (d, 1H), 6.53 (dd, 1H), 5.90 (dd, 1H), 5.51 (dd, 1H), 3.44 – 3.26 (m, 2H), 2.97 – 2.76 (m, 8H), 2.60 (dd, 1H), 2.38 (dd, 1H), 2.30 (s, 3H), 2.29 – 2.11 (m, 4H), 1.88 (s, 3H), 1.60 – 1.04 (m, 11H), 1.03 – 0.94 (m, 2H), 0.76 – 0.61 (m, 2H). LCMS (Method 15): 2.01 min, 630.3 $[M+H]^+$. **Example 95:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.82 (s, 1H), 7.46 (d, 1H), 7.10 (d, 1H), 6.91 (s, 1H), 6.88 (s, 1H), 6.64 – 6.47 (m, 2H), 5.77 (dd, 1H), 5.46 (dd, 1H), 2.74 – 2.62 (m, 5H), 2.61 – 2.51 (m, 1H), 2.42 (s, 6H), 2.31 (s, 3H), 2.30 – 2.23 (m, 1H), 2.21 – 2.12 (m, 1H), 2.04 – 1.95 (m, 1H), 1.94 (s, 3H), 1.67 –

1.54 (m, 1H), 1.41 – 1.06 (m, 8H), 1.05 – 0.98 (m, 2H), 0.97 – 0.84 (m, 1H), 0.77 – 0.64 (m, 2H). LCMS (Method 15): 1.79 min, 616.3 $[M+H]^+$.

**Example 96:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$,2$^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

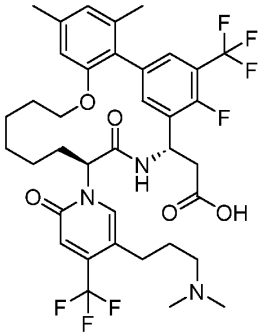


**Example 97:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$,2$^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



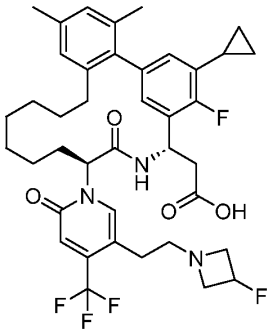
**[001444]** Prepared in an analogous manner to **Example 27** using **Intermediate 563** (0.13 g, 0.07 mmol) and lithium hydroxide (5 mg, 0.21 mmol) in THF (1.6 mL), MeOH (0.6 mL) and water (0.3 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 96** (13 mg), and **Example 97** (12 mg). **Example 96:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.90 (s, 1H), 7.05 (dd, 1H), 6.93 (s, 1H), 6.89 (s, 2H), 6.87 (dd, 1H), 5.95 (dd, 1H), 5.46 (dd, 1H), 3.44 – 3.24 (m, 2H), 3.08 – 2.95 (m, 2H), 2.92 (s, 6H), 2.65 (dd, 1H), 2.51 (dd, 1H), 2.38 – 2.14 (m, 9H), 1.92 (s, 3H), 1.69 – 0.83 (m, 11H). LCMS (Method 15): 1.82 min, 672.3 $[M+H]^+$. **Example 97:** $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.05 (s, 1H), 7.08 (dd, 1H), 6.91 (s, 1H), 6.89 – 6.81 (m, 3H), 5.81 (dd, 1H), 5.42 (dd, 1H), 3.08 – 2.73 (m, 4H), 2.71 – 2.41 (m, 8H), 2.38 – 2.16 (m, 7H), 2.02 – 1.90 (m, 4H), 1.70 – 1.58 (m, 1H), 1.47 – 0.81 (m, 9H). LCMS (Method 11): 1.50 min, 656.5 $[M-H]^-$.

**Example 98:** 2-((10*S*,13*S*)-10-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001445]** Prepared in an analogous manner to **Example 27** using **Intermediate 568** (0.17 g, 0.22 mmol) and lithium hydroxide (7.9 mg, 0.33 mmol) in THF (7 mL), MeOH (7 mL) and water (3.5 mL) at RT for 3 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (12 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.95 (s, 1H), 7.56 (dd, 1H), 7.32 (d, 1H), 6.84 (s, 1H), 6.79 (s, 1H), 6.76 (s, 1H), 6.09 – 5.86 (m, 1H), 5.58 – 5.38 (m, 1H), 4.06 – 3.83 (m, 2H), 3.04 – 2.88 (m, 2H), 2.74 (s, 6H), 2.72 – 2.48 (m, 3H), 2.34 (s, 3H), 2.16 – 2.01 (m, 3H), 1.99 (s, 3H), 1.68 – 1.57 (m, 1H), 1.56 – 1.46 (m, 2H), 1.44 – 0.96 (m, 7H). LCMS (Method 15): 1.78 min, 742.3 $[M+H]^+$.

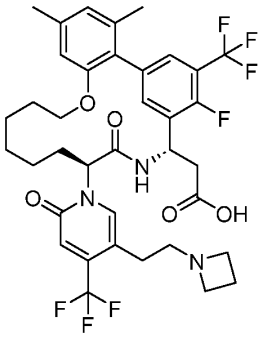
**Example 99:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-2$^4$-fluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001446]** Prepared in an analogous manner to **Example 27** using **Intermediate 571** (0.12 g, 0.16 mmol) and lithium hydroxide (5.6 mg, 0.23 mmol) in THF (4.8 mL), MeOH (4.8 mL) and water (2.4 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (34 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.84 (s, 1H), 7.02 (dd, 1H), 6.92 (s, 1H),

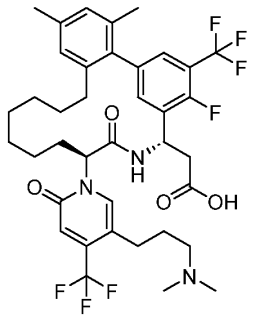
6.89 (s, 2H), 6.55 (dd, 1H), 5.97 (dd, 1H), 5.49 (dd, 1H), 5.46 – 5.25 (m, 1H), 4.55 –4.39 (m, 2H), 4.27 – 4.05 (m, 2H), 3.41 (t, 2H), 2.94 (dt, 1H), 2.78 (dt, 1H), 2.67 (dd, 1H), 2.49 (dd, 1H), 2.35 – 2.11 (m, 7H), 1.90 (s, 3H), 1.67 – 1.46 (m, 2H), 1.44 – 0.85 (m, 11H), 0.78 – 0.64 (m, 2H). LCMS (Method 15): 1.95 min, 728.3 $[M+H]^+$.

**Example 100:** 2-((10*S*,13*S*)-10-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



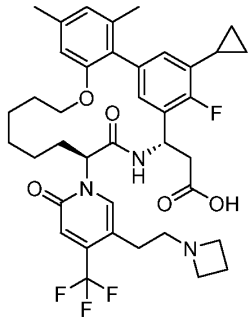
**[001447]** Prepared in an analogous manner to **Example 27** using **Intermediate 574** (0.12 g, 0.15 mmol) and lithium hydroxide (5.5 mg, 0.23 mmol) in THF (2.7 mL), MeOH (2.7 mL) and water (1.4 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (38 mg). $^1$H NMR (500 MHz, $CD_3OD$) δ: 7.88 (s, 1H), 7.58 (d, 1H), 7.33 (d, 1H), 6.87 (s, 1H), 6.79 (s, 1H), 6.76 (s, 1H), 6.06 – 5.90 (m, 1H), 5.60 – 5.43 (m, 1H), 4.20 – 3.80 (m, 6H), 3.31 – 3.19 (m, 2H), 2.94 – 2.80 (m, 1H), 2.79 – 2.69 (m, 1H), 2.68 – 2.60 (m, 1H), 2.59 – 2.49 (m, 1H), 2.48 – 2.37 (m, 2H), 2.34 (s, 3H), 2.19 – 2.09 (m, 1H), 2.02 (s, 3H), 1.66 – 1.47 (m, 3H), 1.45 – 1.09 (m, 6H). LCMS (Method 11): 1.63 min, 738.5 $[M-H]^-$.

**Example 101:** 2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



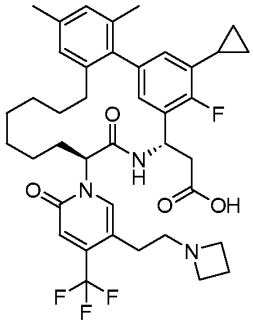
**[001448]** Prepared in an analogous manner to **Example 27** using **Intermediate 576** (74 mg, 0.10 mmol) and lithium hydroxide (3.5 mg, 0.15 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.2 mL) at RT for 1 h. Purified by reverse phase chromatography (32 g C18, 30-70% MeCN in 0.1% aqueous ammonia) to provide the title compound (18 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.86 (s, 1H), 7.55 (dd, 1H), 7.28 (dd, 1H), 6.98 (s, 1H), 6.95 (s, 1H), 6.85 (s, 1H), 6.03 (dd, 1H), 5.46 (dd, 1H), 3.44 – 3.22 (m, 2H), 2.92 – 2.79 (m, 2H), 2.74 – 2.35 (m, 11H), 2.32 (s, 1H), 2.29 – 2.14 (m, 2H), 2.11 – 1.94 (m, 2H), 1.93 (s, 3H), 1.62 – 0.84 (m, 11H). LCMS (Method 15): 2.30 min, 740.3 $[M+H]^+$.

**Example 102:** 2-((10*S*,13*S*)-10-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^5$-cyclopropyl-1$^4$-fluoro-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



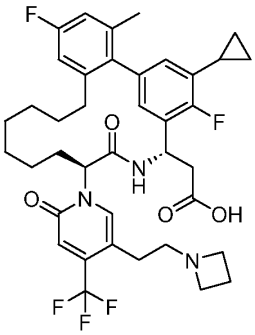
**[001449]** Prepared in an analogous manner to **Example 27** using **Intermediate 580** (89 mg, 0.11 mmol) and lithium hydroxide (3.8 mg, 0.16 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.2 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (40 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.95 (s, 1H), 7.10 (d, 1H), 6.87 (s, 1H), 6.75 (d, 1H), 6.74 (s, 1H), 6.60 (d, 1H), 6.06 – 5.90 (m, 1H), 5.60 – 5.48 (m, 1H), 4.05 – 3.54 (m, 6H), 3.24 – 3.02 (m, 2H), 2.97 – 2.48 (m, 4H), 2.46 – 2.35 (m, 2H), 2.34 (s, 3H), 2.21 – 2.07 (m, 2H), 1.98 (s, 3H), 1.67 – 1.13 (m, 9H), 1.06 – 0.92 (m, 2H), 0.78 – 0.63 (m, 2H). LCMS (Method 15): 1.73 min, 712.3 $[M+H]^+$.

**Example 103:** 2-((3*S*,6S)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



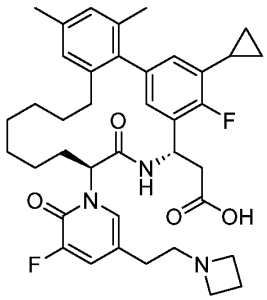
**[001450]** Prepared in an analogous manner to **Example 27** using **Intermediate 584** (71 mg, 0.09 mmol) and lithium hydroxide (3.0 mg, 0.13 mmol) in THF (0.8 mL), MeOH (0.4 mL) and water (0.2 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (37 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.83 (s, 1H), 7.04 (dd, 1H), 6.96 – 6.87 (m, 3H), 6.55 (d, 1H), 6.00 (dd, 1H), 5.52 (dd, 1H), 4.25 – 3.90 (m, 4H), 3.42 – 3.21 (m, 2H), 3.00 – 2.86 (m, 1H), 2.83 – 2.69 (m, 1H), 2.66 (dd, 1H), 2.56 – 2.40 (m, 3H), 2.32 (s, 3H), 2.31 – 2.12 (m, 4H), 1.92 (s, 3H), 1.62 – 1.47 (m, 2H), 1.46 – 0.89 (m, 11H), 0.79 – 0.65 (m, 2H). LCMS (Method 15): 1.73 min, 710.3 $[M+H]^+$.

**Example 104:** 2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



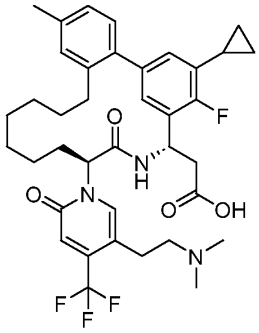
**[001451]** Prepared in an analogous manner to **Example 27** using **Intermediate 590** (71 mg, 0.08 mmol) and lithium hydroxide (3.0 mg, 0.13 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.2 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (18 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.84 (s, 1H), 7.05 (dd, 1H), 6.92 – 6.81 (m, 3H), 6.58 (d, 1H), 6.00 (dd, 1H), 5.53 (dd, 1H), 4.14 – 3.85 (m, 4H), 3.32 – 3.19 (m, 2H), 2.97 – 2.83 (m, 1H), 2.78 – 2.68 (m, 1H), 2.65 (dd, 1H), 2.50 – 2.31 (m, 4H), 2.30 – 2.14 (m, 3H), 1.97 (s, 3H), 1.66 – 1.48 (m, 2H), 1.47 – 0.85 (m, 11H), 0.79 – 0.65 (m, 2H). LCMS (Method 15): 2.06 min, 714.2 $[M+H]^+$.

**Example 105:** 2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001452]** Prepared in an analogous manner to **Example 27** using **Intermediate 595** (79 mg, 0.07 mmol) and lithium hydroxide (2.5 mg, 0.10 mmol) in THF (2 mL), MeOH (0.8 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (14 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.45 (s, 1H), 7.36 (dd, 1H), 7.04 (dd, 1H), 6.94 (s, 1H), 6.91 (s, 1H), 6.55 (dd, 1H), 5.94 (dd, 1H), 5.57 (dd, 1H), 4.20 – 3.83 (m, 4H), 3.37 – 3.28 (m, 2H), 2.83 – 2.65 (m, 2H), 2.64 (dd, 1H), 2.51 – 2.38 (m, 3H), 2.32 (s, 3H), 2.31 – 2.24 (m, 2H), 2.23 – 2.12 (m, 2H), 1.91 (s, 3H), 1.63 – 1.47 (m, 2H), 1.46 – 0.89 (m, 11H), 0.77 – 0.63 (m, 2H). LCMS (Method 15): 1.97 min, 660.3 $[M+H]^+$.

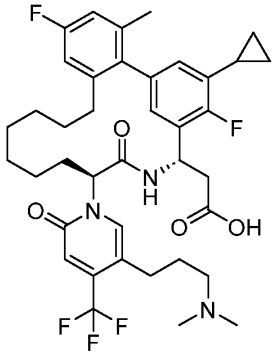
**Example 106:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001453]** Prepared in an analogous manner to **Example 27** using **Intermediate 603** (0.13 g, 0.09 mmol) and lithium hydroxide (47 mg, 3.97 mmol) in THF (1 mL), MeOH (1 mL) and water (1 mL) at RT for 2 h. Purified by reverse phase chromatography (55 g C18, 30-70% MeCN in 0.1% aqueous formic acid) and preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 22 min) to provide the title compound (15 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.98 (s, 1H), 7.19 (dd, 1H), 7.10 (s, 1H), 7.03 (s, 2H),

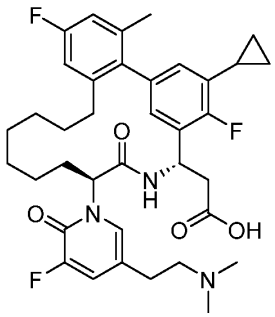
6.87 (s, 1H), 6.68 (dd, 1H), 5.90 (dd, 1H), 5.49 (dd, 1H), 2.99 – 2.77 (m, 4H), 2.67 (dd, 1H), 2.64 – 2.57 (m, 1H), 2.56 (s, 6H), 2.55 – 2.43 (m, 1H), 2.37 (s, 3H), 2.22 – 2.10 (m, 2H), 1.65 – 1.53 (m, 1H), 1.52 – 1.30 (m, 4H), 1.29 – 0.89 (m, 9H), 0.77 – 0.67 (m, 2H). LCMS (Method 15): 1.92 min, 682.3 $[M-H]^-$.

**Example 107:** 2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



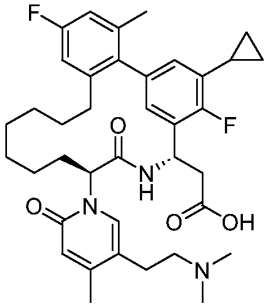
**[001454]** Prepared in an analogous manner to **Example 27** using **Intermediate 605** (80 mg, 0.11 mmol) and lithium hydroxide (3.9 mg, 0.16 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.2 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (10 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.91 (s, 1H), 7.04 (dd, 1H), 6.87 (dd, 1H), 6.86 (s, 1H), 6.84 (dd, 1H), 6.57 (dd, 1H), 6.07 (dd, 1H), 5.45 (dd, 1H), 3.01 – 2.88 (m, 2H), 2.76 (s, 6H), 2.75 – 2.68 (m, 2H), 2.65 – 2.51 (m, 2H), 2.44 – 2.27 (m, 3H), 2.26 – 1.97 (m, 4H), 1.96 (s, 3H), 1.68 – 0.86 (m, 12H), 0.79 – 0.67 (m, 2H). LCMS (Method 15): 2.20 min, 716.2 $[M+H]^+$.

**Example 108:** 2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



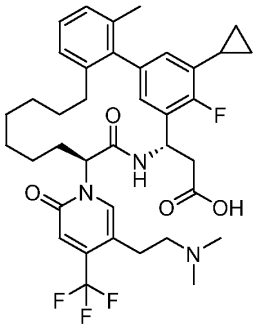
**[001455]** Prepared in an analogous manner to **Example 27** using **Intermediate 608** (92 mg, 0.10 mmol) and lithium hydroxide (3.6 mg, 0.15 mmol) in THF (2.1 mL), MeOH (2.1 mL) and water (1.1 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (39 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.52 (s, 1H), 7.41 (dd, 1H), 7.03 (dd, 1H), 6.90 – 6.80 (m, 2H), 6.57 (dd, 1H), 5.91 (dd, 1H), 5.56 (dd, 1H), 3.32 – 3.17 (m, 2H), 2.99 – 2.88 (m, 1H), 2.86 – 2.80 (m, 1H), 2.79 (s, 6H), 2.60 (dd, 1H), 2.40 – 2.29 (m, 3H), 2.27 – 2.13 (m, 2H), 1.95 (s, 3H), 1.66 – 1.49 (m, 2H), 1.48 – 0.90 (m, 11H), 0.80 – 0.65 (m, 2H). LCMS (Method 11): 1.89 min, 652.2 $[M+H]^+$.

**Example 109:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

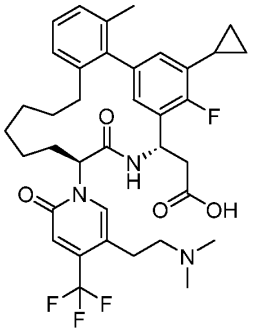


**[001456]** Prepared in an analogous manner to **Example 27** using **Intermediate 611** (70 mg, 84 µmol) and lithium hydroxide (3.0 mg, 0.13 mmol) in THF (1.3 mL), MeOH (1.3 mL) and water (0.6 mL) at RT for 3 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (26 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.60 (s, 1H), 7.05 (dd, 1H), 6.86 (dd, 1H), 6.83 (dd, 1H), 6.56 (dd, 1H), 6.44 (s, 1H), 5.93 (dd, 1H), 5.49 (dd, 1H), 3.25 – 3.13 (m, 1H), 3.11 – 3.00 (m, 1H), 2.96 – 2.75 (m, 3H), 2.75 (s, 6H), 2.61 (dd, 1H), 2.41 (dd, 1H), 2.38 – 2.27 (m, 1H), 2.27 (s, 3H), 2.26 – 2.13 (m, 2H), 1.96 (s, 3H), 1.61 – 1.45 (m, 2H), 1.44 – 0.89 (m, 11H), 0.79 – 0.64 (m, 2H). LCMS (Method 11): 1.73 min, 648.3 $[M+H]^+$.

**Example 110:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

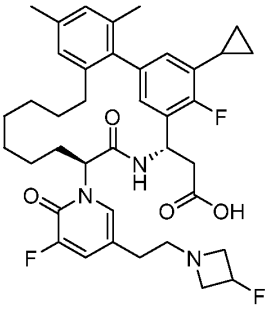


**Example 111:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



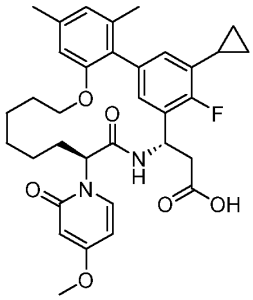
**[001457]** Prepared in an analogous manner to **Example 27** using **Intermediate 620** (83 mg, 0.12 mmol) and lithium hydroxide (8.4 mg, 0.35 mmol) in THF (2.8 mL), MeOH (1.4 mL) and water (1.4 mL) at RT for 2.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 110** (16 mg), and **Example 111** (9 mg). **Example 110**: $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.94 (s, 1H), 7.20 – 7.03 (m, 4H), 6.86 (s, 1H), 6.55 (dd, 1H), 5.91 (dd, 1H), 5.51 (dd, 1H), 2.95 – 2.68 (m, 4H), 2.64 (dd, 1H), 2.58 – 2.50 (m, 2H), 2.49 (s, 6H), 2.42 – 2.32 (m, 2H), 2.27 – 2.14 (m, 2H), 1.97 (s, 3H), 1.67 – 0.86 (m, 12H), 0.79 – 0.65 (m, 2H). LCMS (Method 15): 1.77 min, 684.3 $[M+H]^+$. **Example 111**: $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.04 (s, 1H), 7.18 – 7.03 (m, 4H), 6.83 (s, 1H), 6.58 (dd, 1H), 5.80 (dd, 1H), 5.47 (dd, 1H), 2.85 – 2.74 (m, 2H), 2.73 – 2.54 (m, 4H), 2.40 (s, 6H), 2.37 – 2.28 (m, 1H), 2.24 – 2.14 (m, 1H), 2.04 – 1.92 (m, 4H), 1.70 – 1.59 (m, 1H), 1.56 – 0.86 (m, 11H), 0.80 – 0.64 (m, 2H). LCMS (Method 15): 1.77 min, 670.3 $[M+H]^+$.

**Example 112:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-2$^4$-fluoro-6-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



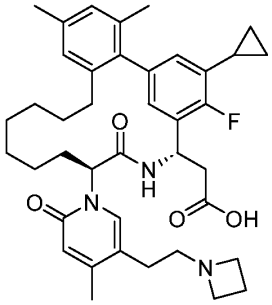
**[001458]** Prepared in an analogous manner to **Example 27** using **Intermediate 622** (49 mg, 69 μmol) and lithium hydroxide (2.5 mg, 0.10 mmol) in THF (1.2 mL), MeOH (0.5 mL) and water (0.3 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (17 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.53 (s, 1H), 7.34 (dd, 1H), 7.08 (dd, 1H), 6.93 (s, 1H), 6.90 (s, 1H), 6.53 (dd, 1H), 5.88 (dd, 1H), 5.55 (dd, 1H), 5.32 – 5.07 (m, 1H), 4.05 – 3.82 (m, 2H), 3.65 – 3.44 (m, 2H), 3.06 – 2.88 (m, 2H), 2.69 – 2.46 (m, 4H), 2.41 – 2.32 (m, 1H), 2.32 (s, 3H), 2.28 – 2.12 (m, 2H), 1.93 (s, 3H), 1.62 – 0.90 (m, 14H), 0.79 – 0.63 (m, 2H). LCMS (Method 15): 1.90 min, 678.3 $[M+H]^+$.

**Example 113:** 2-((10*S*,13*S*)-1$^5$-Cyclopropyl-1$^4$-fluoro-10-(4-methoxy-2-oxopyridin-1(2*H*)-yl)-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



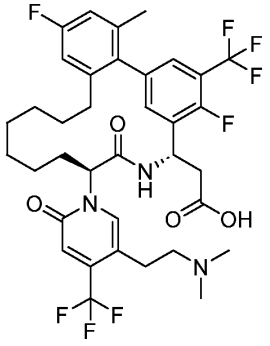
**[001459]** Prepared in an analogous manner to **Example 27** using **Intermediate 625** (38 mg, 63 μmol) and lithium hydroxide (2.3 mg, 94 μmol) in THF (1.0 mL), MeOH (1.0 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (15 mg). $^1$H NMR (500 MHz, $CD_3OD$) δ: 7.81 (d, 1H), 7.12 (d, 1H), 6.79 – 6.64 (m, 2H), 6.57 (d, 1H), 6.12 (d, 1H), 5.95 – 5.87 (m, 2H), 5.51 – 5.29 (m, 1H), 4.03 – 3.94 (m, 1H), 3.92 – 3.84 (m, 1H), 3.83 (s, 3H), 2.81 – 2.68 (m, 2H), 2.33 (s, 3H), 2.20 – 1.97 (m, 2H), 1.96 (s, 3H), 1.64 – 1.08 (m, 9H), 1.06 – 0.85 (m, 2H), 0.80 – 0.60 (m, 2H). LCMS (Method 15): 1.55 min, 591.2 $[M+H]^+$.

**Example 114:** 2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

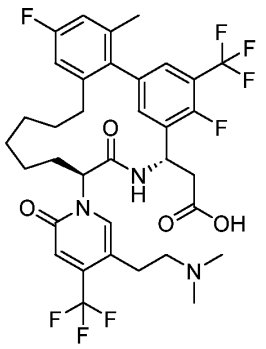


**[001460]** Prepared in an analogous manner to **Example 27** using **Intermediate 631** (27 mg, 39 µmol) and lithium hydroxide (1.9 mg, 79 µmol) in THF (1.0 mL), MeOH (0.2 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (17 mg). $^1$H NMR (500 MHz, $CD_3OD$) δ: 7.55 (s, 1H), 7.06 (dd, 1H), 6.93 (s, 1H), 6.90 (s, 1H), 6.54 (dd, 1H), 6.43 (s, 1H), 5.94 (dd, 1H), 5.51 (dd, 1H), 4.76 – 4.44 (br m, 2H), 4.17 – 3.56 (br m, 4H), 3.30 – 3.02 (br m, 1H), 2.91 – 2.70 (br m, 1H), 2.64 (dd, 1H), 2.62 – 2.53 (m, 1H), 2.51 – 2.33 (m, 2H), 2.32 (s, 3H), 2.31 – 2.24 (m, 2H), 2.25 (s, 3H), 2.21 – 2.14 (m, 1H), 1.92 (s, 3H), 1.60 – 1.44 (m, 2H), 1.44 – 0.91 (m, 12H), 0.77 – 0.64 (m, 2H). LCMS (Method 15): 2.12 min, 656.3 $[M+H]^+$.

**Example 115:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

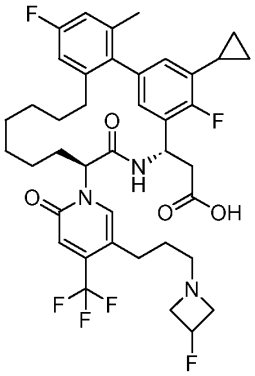


**Example 116:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



**[001461]** Prepared in an analogous manner to **Example 27** using **Intermediate 641** (0.15 g, 0.12 mmol) and lithium hydroxide (4.2 mg, 0.18 mmol) in THF (1.5 mL), MeOH (0.7 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 115** (32 mg), and **Example 116** (4 mg). Example **115**: $^1$H NMR (400 MHz; DMSO-$d_6$) δ: 9.71 (br s, 1H), 7.89 (s, 1H), 7.74 (dd, 1H), 7.38 (dd, 1H), 7.04 (dd, 1H), 7.02 (dd, 1H), 6.77 (s, 1H), 5.64 (dd, 1H), 5.36 (dd, 1H), 2.66 – 2.57 (m, 2H), 2.50 – 2.34 (m, 4H), 2.30 – 2.23 (m, 1H), 2.23 (s, 6H), 2.14 – 2.00 (m, 1H), 1.92 (s, 3H), 1.50 – 1.38 (m, 2H), 1.37 – 0.82 (m, 10H) – OH not observed. LCMS (Method 15): 1.86 min, 730.2 $[M+H]^+$. **Example 116**: $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 10.19 (br s, 1H), 8.00 (s, 1H), 7.66 (d, 1H), 7.40 (d, 1H), 7.02 (dd, 1H), 6.96 (dd, 1H), 6.73 (s, 1H), 5.44 (dd, 1H), 5.31 (dd, 1H), 2.65 – 2.11 (m, 6H), 2.17 (s, 6H), 1.93 (s, 3H), 1.91 – 1.70 (m, 2H), 1.54 – 1.40 (m, 2H), 1.37 – 0.82 (m, 8H) – OH not observed. LCMS (Method 15): 1.74 min, 716.2 $[M+H]^+$.

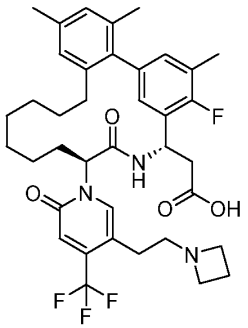
**Example 117:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(3-(3-fluoroazetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001462]** Prepared in an analogous manner to **Example 27** using **Intermediate 644** (78 mg, 0.10 mmol) and lithium hydroxide (3.6 mg, 0.15 mmol) in THF (1.0 mL), MeOH (0.5 mL) and water (0.2 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5

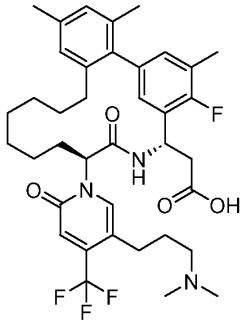
μm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (17 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.89 (s, 1H), 7.07 (dd, 1H), 6.86 – 6.78 (m, 3H), 6.53 (dd, 1H), 5.91 (dd, 1H), 5.48 (dd, 1H), 5.32 – 5.09 (m, 1H), 4.00 – 3.75 (m, 2H), 3.66 – 3.44 (m, 2H), 2.75 (t, 2H), 2.70 – 2.46 (m, 4H), 2.43 – 2.29 (m, 2H), 2.25 – 2.11 (m, 2H), 1.96 (s, 3H), 1.85 – 1.63 (m, 2H), 1.60 – 0.89 (m, 13H), 0.77 – 0.61 (m, 2H). LCMS (Method 15): 1.99 min, 746.2 $[M+H]^+$.

**Example 118:** 2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$,2$^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



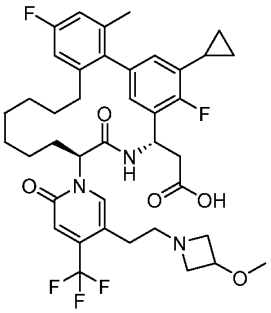
**[001463]** Prepared in an analogous manner to **Example 27** using **Intermediate 649** (0.12 g, 0.17 mmol) and lithium hydroxide (6.1 mg, 0.25 mmol) in THF (4.7 mL), MeOH (2.4 mL) and water (0.9 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (65 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.87 (s, 1H), 7.10 (dd, 1H), 6.94 (s, 1H), 6.91 (s, 1H), 6.87 (s, 1H), 6.85 (dd, 1H), 5.93 (dd, 1H), 5.52 (dd, 1H), 3.93 – 3.66 (br m, 4H), 3.19 – 2.96 (br m, 2H), 2.89 – 2.76 (br m, 1H), 2.70 (dd, 1H), 2.63 (dd, 1H), 2.48 (dd, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 2.31 – 2.14 (m, 4H), 1.95 (s, 3H), 1.60 – 1.47 (m, 2H), 1.45 – 0.98 (m, 10H). LCMS (Method 21): 4.07 min, 684.3 $[M+H]^+$.

**Example 119:** 2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$,2$^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

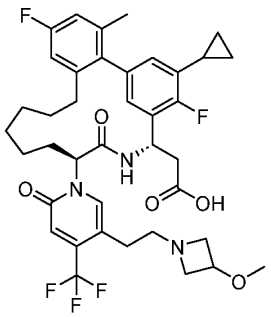


**[001464]** Prepared in an analogous manner to **Example 27** using **Intermediate 651** (0.19 g, 0.22 mmol) and lithium hydroxide (7.8 mg, 0.33 mmol) in THF (2 mL), MeOH (1 mL) and water (0.4 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 45-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (42 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.91 (s, 1H), 7.08 (dd, 1H), 6.94 (s, 1H), 6.91 (s, 1H), 6.86 (dd, 1H), 6.85 (s, 1H), 6.02 (dd, 1H), 5.46 (dd, 1H), 2.95 – 2.81 (m, 2H), 2.76 – 2.58 (m, 2H), 2.70 (s, 6H), 2.55 (dd, 1H), 2.42 (dd, 1H), 2.37 – 2.29 (m, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 2.25 – 2.15 (m, 1H), 2.13 – 2.02 (m, 1H), 2.01 – 1.95 (m, 1H), 1.94 (s, 3H), 1.61 – 0.98 (m, 12H). LCMS (Method 21): 3.87 min, 686.3 $[M+H]^+$.

**Example 120:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

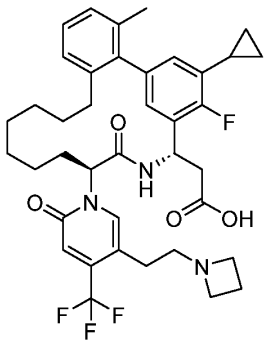


**Example 121:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



**[001465]** Prepared in an analogous manner to **Example 27** using **Intermediate 652** (77 mg, 79 µmol) and lithium hydroxide (8 mg, 0.33 mmol) in THF (1 mL) and water (0.3 mL) at RT for 3 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 120** (17 mg), and **Example 121** (7 mg). **Example 120**: $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.91 (s, 1H), 7.10 (dd, 1H), 6.90 – 6.78 (m, 3H), 6.55 (dd, 1H), 5.90 (dd, 1H), 5.53 (dd, 1H), 4.20 – 4.11 (m, 1H), 4.02 – 3.82 (m, 2H), 3.41 – 3.35 (m, 2H), 3.34 (s, 3H), 3.02 – 2.86 (m, 2H), 2.85 – 2.68 (m, 2H), 2.64 (dd, 1H), 2.52 (dd, 1H), 2.36 (t, 2H), 2.28 – 2.13 (m, 2H), 1.98 (s, 3H), 1.67 – 0.98 (m, 13H), 0.78 – 0.64 (m, 2H). LCMS (Method 15): 1.75 min, 744.3 $[M+H]^+$. **Example 121**: $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.00 (s, 1H), 7.11 (dd, 1H), 6.84 (dd, 1H), 6.82 (s, 1H), 6.81 (dd, 1H), 6.57 (dd, 1H), 5.77 (dd, 1H), 5.47 (dd, 1H), 4.13 – 4.03 (m, 1H), 3.74 – 3.59 (m, 2H), 3.30 (s, 3H), 3.15 – 2.94 (m, 2H), 2.80 – 2.54 (m, 6H), 2.42 – 2.27 (m, 1H), 2.25 – 2.13 (m, 1H), 2.04 – 1.91 (m, 1H), 1.99 (s, 3H), 1.71 – 1.59 (m, 1H), 1.54 – 0.89 (m, 11H), 0.79 – 0.65 (m, 2H). LCMS (Method 15): 1.66 min, 730.3 $[M+H]^+$.

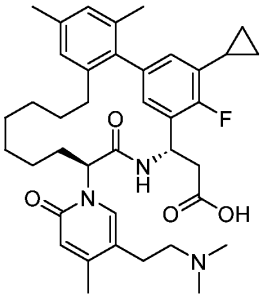
**Example 122:** 2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



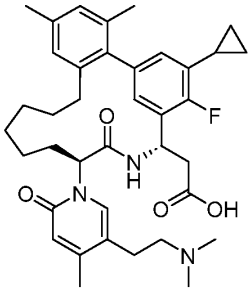
**[001466]** Prepared in an analogous manner to **Example 27** using **Intermediate 658** (0.15 g, 0.20 mmol) and lithium hydroxide (15 mg, 0.61 mmol) in THF (2 mL), MeOH (1 mL) and water (1 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 45-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title

compound (68 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.82 (s, 1H), 7.19 (t, 1H), 7.12 (d, 1H), 7.10 – 7.03 (m, 2H), 6.90 (s, 1H), 6.58 (dd, 1H), 6.03 (dd, 1H), 5.52 (dd, 1H), 4.25 – 3.95 (m, 4H), 3.47 – 3.34 (m, 2H), 3.01 – 2.90 (m, 1H), 2.81 – 2.70 (dd, 1H), 2.66 (dd, 1H), 2.56 – 2.14 (m, 7H), 1.96 (s, 3H), 1.66 – 1.47 (m, 2H), 1.46 – 0.92 (m, 11H), 0.80 – 0.66 (m, 2H). LCMS (Method 15): 2.02 min, 696.3 $[M+H]^+$.

**Example 123:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



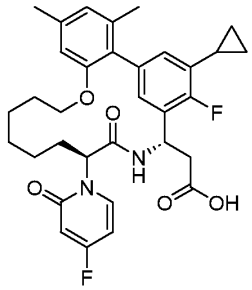
**Example 124:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



**[001467]** Prepared in an analogous manner to **Example 27** using **Intermediate 661** (94 mg, 96 μmol) and lithium hydroxide (4.6 mg, 0.19 mmol) in THF (1.5 mL), MeOH (1.0 mL) and water (0.8 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 123** (35 mg), and **Example 124** (5 mg). **Example 123**: $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.61 (s, 1H), 7.04 (dd, 1H), 6.93 (s, 1H), 6.90 (s, 1H), 6.53 (dd, 1H), 6.44 (s, 1H), 5.92 (dd, 1H), 5.48 (dd, 1H), 3.21 – 2.96 (m, 2H), 2.93 – 2.76 (m, 2H), 2.72 (s, 6H), 2.61 (dd, 1H), 2.42 (dd, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 2.27 – 2.13 (m, 3H), 1.92 (s, 3H), 1.62 – 1.46 (m, 2H), 1.44 – 0.89 (m, 12H), 0.76 – 0.66 (m, 2H). LCMS (Method 15): 1.82 min, 644.3 $[M+H]^+$. **Example 124**: $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.74 (s, 1H), 7.10 (dd, 1H), 6.91 (s, 1H), 6.87 (s, 1H), 6.55 (dd, 1H), 6.39 (s, 1H), 5.77 (dd, 1H), 5.44 (dd, 1H), 2.73 – 2.63 (m, 3H), 2.62 – 2.51 (m, 3H), 2.40

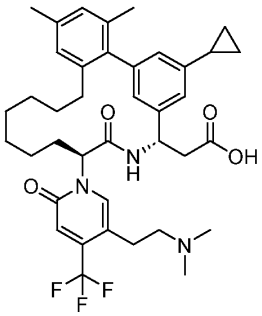
(s, 6H), 2.31 (s, 3H), 2.26 (s, 3H), 2.24 – 2.13 (m, 2H), 2.00 – 1.96 (m, 1H), 1.95 (s, 3H), 1.67 – 0.85 (m, 12H), 0.78 – 0.64 (m, 2H). LCMS (Method 15): 1.69 min, 630.3 $[M+H]^+$.

**Example 125:** 2-((10*S*,13*S*)-$1^5$-cyclopropyl-$1^4$-fluoro-10-(4-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001468]** Prepared in an analogous manner to **Example 27** using **Intermediate 625** (38 mg, 63 µmol) and lithium hydroxide (4.5 mg, 0.19 mmol) in THF (1 mL), and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-60% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (17 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.05 (t, 1H), 7.11 (d, 1H), 6.72 (s, 2H), 6.57 (d, 1H), 6.35 (t, 1H), 6.19 (dd, 1H), 5.92 (t, 1H), 5.53 – 5.37 (m, 1H), 4.02 – 3.93 (m, 1H), 3.92 – 3.81 (m, 1H), 2.89 – 2.54 (m, 2H), 2.33 (s, 3H), 2.21 – 2.08 (m, 1H), 2.05 – 1.97 (m, 1H), 1.96 (s, 3H), 1.68 – 1.44 (m, 3H), 1.43 – 1.08 (m, 6H), 1.04 – 0.95 (m, 2H), 0.75 – 0.64 (m, 2H). LCMS (Method 15): 1.40 min, 579.2 $[M+H]^+$.

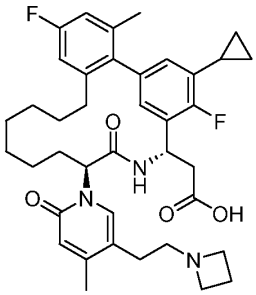
**Example 126:** 2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001469]** Prepared in an analogous manner to **Example 27** using **Intermediate 675** (59 mg, 78 µmol) and lithium hydroxide (5.6 mg, 0.123 mmol) in THF (1.9 mL), MeOH (0.9 mL) and water (0.9 mL) at RT for 3.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (18 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.96 (s, 1H), 7.09 (s, 1H), 7.03 (s, 1H),

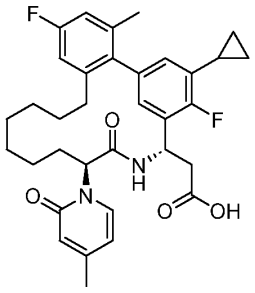
6.93 (s, 1H), 6.91 (s, 1H), 6.87 (s, 1H), 6.70 (s, 1H), 5.64 – 5.29 (m, 2H), 3.08 – 2.83 (m, 4H), 2.63 (s, 6H), 2.62 – 2.42 (m, 2H), 2.40 – 2.23 (m, 4H), 2.23 – 2.11 (m, 1H), 2.03 – 1.95 (m, 1H), 1.95 (s, 3H), 1.65 – 1.13 (m, 10H), 1.13 – 0.89 (m, 4H), 0.82 – 0.67 (m, 2H). LCMS (Method 21): 3.70 min, 680.3 $[M+H]^+$.

**Example 127:** 2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001470]** Prepared in an analogous manner to **Example 27** using **Intermediate 681** (0.12 g, 0.12 mmol) and lithium hydroxide (5.9 mg, 0.24 mmol) in THF (1.9 mL), MeOH (1.3 mL) and water (1.0 mL) at RT for 3.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (1.6 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.52 (s, 1H), 7.04 (dd, 1H), 6.93 – 6.79 (m, 2H), 6.57 (dd, 1H), 6.44 (s, 1H), 5.97 (dd, 1H), 5.53 (dd, 1H), 4.23 – 3.82 (m, 4H), 2.97 – 2.71 (m, 1H), 2.70 – 2.54 (m, 2H), 2.53 – 2.27 (m, 5H), 2.25 (s, 3H), 2.25 – 2.13 (m, 3H), 1.96 (s, 3H), 1.67 – 1.15 (m, 10H), 1.15 – 0.86 (m, 4H), 0.82 – 0.65 (m, 2H). LCMS (Method 15): 1.85 min, 660.3 $[M+H]^+$.

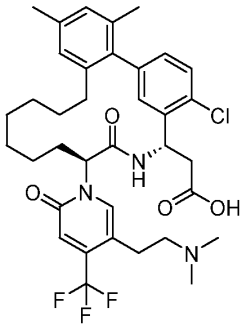
**Example 128:** 2-((3*S*,6*S*)-$2^5$-Cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-6-(4-methyl-2-oxopyridin-1(2*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001471]** Prepared in an analogous manner to **Example 27** using **Intermediate 682** (0.11 g, 0.16 mmol) and lithium hydroxide (7.8 mg, 0.32 mmol) in THF (1.6 mL), MeOH (1.1 mL) and water (0.8 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title

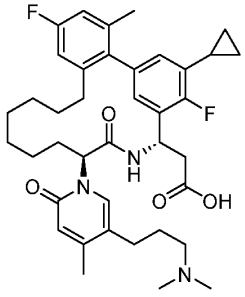
compound (1.6 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.73 (d, 1H), 7.10 (dd, 1H), 6.89 – 6.79 (m, 2H), 6.56 (dd, 1H), 6.38 (s, 1H), 6.31 (dd, 1H), 5.88 (dd, 1H), 5.48 (dd, 1H), 2.68 (dd, 1H), 2.62 (dd, 1H), 2.46 – 2.30 (m, 2H), 2.23 (s, 3H), 2.23 – 2.12 (m, 2H), 2.11 – 2.01 (m, 1H), 1.98 (s, 3H), 1.65 – 0.96 (m, 12H), 0.81 – 0.64 (m, 2H). LCMS (Method 15): 1.64 min, 577.2 $[M+H]^+$.

**Example 129:** 2-((3*S*,6*S*)-2$^4$-Chloro-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001472]** Prepared in an analogous manner to **Example 27** using **Intermediate 696** (60 mg, 65 μmol) and lithium hydroxide (6.6 mg, 0.28 mmol) in THF (0.6 mL) and water (0.2 mL) at RT for 3 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (18 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.91 (s, 1H), 7.45 (d, 1H), 7.37 (d, 1H), 6.97 (dd, 1H), 6.96 (s, 1H), 6.92 (s, 1H), 6.87 (s, 1H), 5.98 (dd, 1H), 5.51 (dd, 1H), 2.97 – 2.70 (m, 4H), 2.62 (dd, 1H), 2.51 (s, 6H), 2.46 (dd, 1H), 2.41 – 2.33 (m, 2H), 2.33 (s, 3H), 2.28 – 2.15 (m, 1H), 1.95 (s, 3H), 1.62 – 1.20 (m, 9H), 1.19 – 0.86 (m, 2H). LCMS (Method 15): 1.86 min, 674.2 $[M+H]^+$.

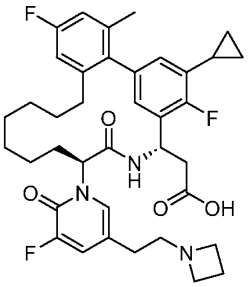
**Example 130:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001473]** Prepared in an analogous manner to **Example 27** using **Intermediate 698** (30 mg, 43 μmol) and lithium hydroxide (2.1 mg, 87 μmol) in THF (0.4 mL), MeOH (0.2 mL) and water (0.2 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm,

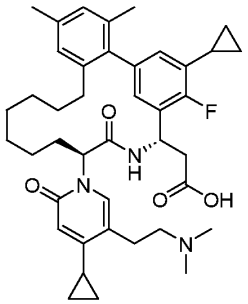
eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (25 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.59 (s, 1H), 7.08 (dd, 1H), 6.89 – 6.78 (m, 2H), 6.54 (dd, 1H), 6.41 (s, 1H), 5.93 (dd, 1H), 5.47 (dd, 1H), 2.79 – 2.63 (br m, 2H), 2.59 (dd, 1H), 2.54 (s, 6H), 2.54 – 2.42 (m, 3H), 2.40 – 2.30 (m, 3H), 2.24 (s, 3H), 2.23 – 2.14 (m, 2H), 1.97 (s, 3H), 1.94 – 1.78 (m, 2H), 1.59 – 0.88 (m, 12H), 0.79 – 0.63 (m, 2H). LCMS (Method 15): 1.88 min, 662.3 $[M+H]^+$.

**Example 131:** 2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



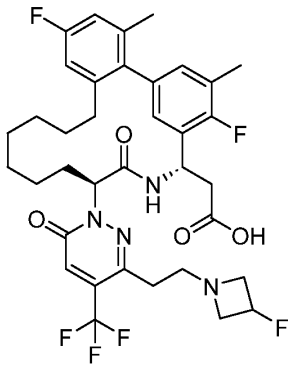
**[001474]** Prepared in an analogous manner to **Example 27** using **Intermediate 704** (0.15 g, 0.21 mmol) and lithium hydroxide (7.5 mg, 0.31 mmol) in THF (3.8 mL), MeOH (1.5 mL) and water (1.0 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (26 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.46 (s, 1H), 7.35 (dd, 1H), 7.05 (dd, 1H), 6.90 – 6.80 (m, 2H), 6.57 (dd, 1H), 5.93 (dd, 1H), 5.57 (dd, 1H), 4.18 – 3.63 (br m, 4H), 3.33 – 3.17 (br m, 2H), 2.77 – 2.57 (m, 3H), 2.49 – 2.12 (m, 6H), 1.96 (s, 3H), 1.63 – 1.47 (m, 2H), 1.46 – 0.89 (m, 12H), 0.81 – 0.64 (m, 2H). LCMS (Method 15): 1.91 min, 664.3 $[M+H]^+$.

**Example 132:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(4-cyclopropyl-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



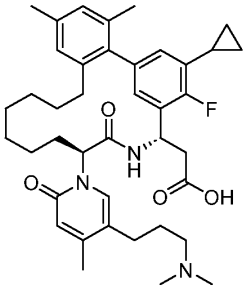
**[001475]** Prepared in an analogous manner to **Example 27** using **Intermediate 712** (0.13 g, 0.15 mmol) and lithium hydroxide (10.6 mg, 0.44 mmol) in THF (3.7 mL), MeOH (2.1 mL) and water (2.1 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (47 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.61 (s, 1H), 7.05 (dd, 1H), 6.93 (s, 1H), 6.90 (s, 1H), 6.53 (dd, 1H), 6.10 (s, 1H), 5.92 (dd, 1H), 5.45 (dd, 1H), 3.20 – 2.80 (m, 4H), 2.68 (s, 6H), 2.62 (dd, 1H), 2.45 (dd, 1H), 2.32 (s, 3H), 2.31 – 2.12 (m, 3H), 1.92 (s, 3H), 1.91 – 1.83 (m, 1H), 1.58 – 1.45 (m, 2H), 1.44 – 0.95 (m, 14H), 0.88 – 0.75 (m, 2H), 0.74 – 0.65 (m, 2H). LCMS (Method 15): 1.88 min, 670.3 $[M+H]^+$.

**Example 133:** 2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



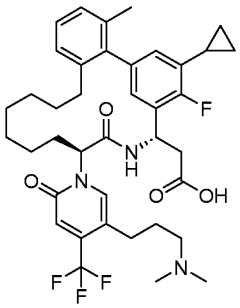
**[001476]** Prepared in an analogous manner to **Example 27** using **Intermediate 1186** (60 mg, 65 µmol) and lithium hydroxide (2.5 mg, 0.10 mmol) in THF (1.0 mL), MeOH (1.0 mL) and water (0.5 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (29 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.41 (s, 1H), 7.13 (dd, 1H), 6.92 – 6.79 (m, 3H), 5.86 (dd, 1H), 5.35 (dd, 1H), 5.31 – 5.08 (m, 1H), 3.95 – 3.70 (m, 2H), 3.55 – 3.37 (m, 2H), 3.15 – 2.97 (m, 2H), 2.96 – 2.82 (m, 2H), 2.72 – 2.54 (m, 2H), 2.49 – 2.34 (m, 2H), 2.33 (s, 3H), 2.32 – 2.20 (m, 1H), 2.00 (s, 3H), 1.92 – 1.76 (m, 1H), 1.57 – 0.88 (m, 10H). LCMS (Method 15): 1.71 min, 707.3 $[M+H]^+$

**Example 134:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



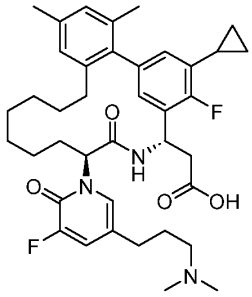
**[001477]** Prepared in an analogous manner to **Example 27** using **Intermediate 725** (36 mg, 51 μmol) and lithium hydroxide (4 mg, 0.17 mmol) in THF (1.0 mL), MeOH (1.0 mL) and water (0.5 mL) at RT for 3 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (12 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.59 (s, 1H), 7.07 (dd, 1H), 6.93 (s, 1H), 6.90 (s, 1H), 6.54 (dd, 1H), 6.41 (s, 1H), 5.94 (dd, 1H), 5.46 (dd, 1H), 2.84 – 2.65 (br m, 2H), 2.63 – 2.43 (m, 11H), 2.40 – 2.26 (m, 5H), 2.23 (s, 3H), 2.22 – 2.13 (m, 2H), 1.92 (s, 3H), 1.91 – 1.79 (m, 2H), 1.56 – 0.96 (m, 12H), 0.79 – 0.64 (m, 2H). LCMS (Method 15): 1.76 min, 658.3 $[M+H]^+$.

**Example 135:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



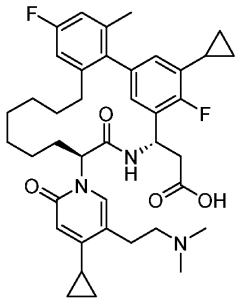
**[001478]** Prepared in an analogous manner to **Example 27** using **Intermediate 727** (0.11 g, 0.15 mmol) and lithium hydroxide (10.6 mg, 0.44 mmol) in THF (1.5 mL), MeOH (0.7 mL) and water (0.7 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (56 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.92 (s, 1H), 7.18 (t, 1H), 7.12 (d, 1H), 7.10 – 7.04 (m, 2H), 6.86 (s, 1H), 6.56 (dd, 1H), 6.03 (dd, 1H), 5.47 (dd, 1H), 2.94 – 2.81 (br m, 2H), 2.77 – 2.58 (m, 8H), 2.58 (dd, 1H), 2.44 (dd, 1H), 2.40 – 2.28 (m, 2H), 2.27 – 2.15 (m, 2H), 2.13 – 1.97 (m, 3H), 1.96 (s, 3H), 1.64 – 0.92 (m, 12H), 0.80 – 0.65 (m, 2H). LCMS (Method 15): 1.99 min, 698.3 $[M+H]^+$.

**Example 136:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001479]** Prepared in an analogous manner to Example **27** using **Intermediate 729** (40 mg, 52 µmol) and lithium hydroxide (4 mg, 0.17 mmol) in THF (1.0 mL), MeOH (1.0 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (26 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.50 (s, 1H), 7.30 (dd, 1H), 7.03 (dd, 1H), 6.94 (s, 1H), 6.90 (s, 1H), 6.54 (dd, 1H), 5.98 (dd, 1H), 5.50 (dd, 1H), 2.95 – 2.80 (br m, 2H), 2.79 – 2.60 (m, 8H), 2.55 (dd, 1H), 2.42 (dd, 1H), 2.38 – 2.13 (m, 8H), 2.10 – 1.92 (m, 2H), 1.91 (s, 3H), 1.60 – 0.89 (m, 12H), 0.78 – 0.65 (m, 2H). LCMS (Method 15): 1.70 min, 662.4 $[M+H]^+$.

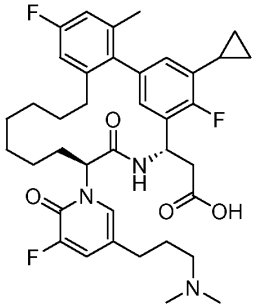
**Example 137:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(4-cyclopropyl-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001480]** Prepared in an analogous manner to **Example 27** using **Intermediate 732** (55 mg, 43 µmol) and lithium hydroxide (3.1 mg, 0.13 mmol) in THF (1.1 mL), MeOH (0.6 mL) and water (0.6 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (17 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.61 (s, 1H), 7.05 (dd, 1H), 6.89 – 6.78 (m, 2H), 6.55 (dd, 1H), 6.10 (s, 1H), 5.92 (dd, 1H), 5.45 (dd, 1H), 3.25 – 2.99 (m, 2H), 2.90 (dd, 1H), 2.70 (s, 6H), 2.62 (dd, 1H), 2.44 (dd, 1H), 2.39 – 2.13 (m, 4H), 1.96 (s, 3H), 1.93 – 1.83 (m, 1H),

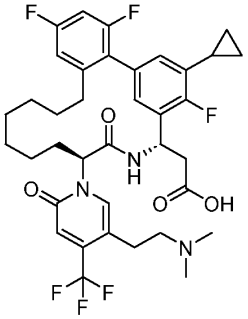
1.62 – 1.46 (m, 2H), 1.45 – 0.97 (m, 14H), 0.88 – 0.76 (m, 2H), 0.75 – 0.65 (m, 2H). LCMS (Method 11): 1.71 min, 674.3 $[M+H]^+$.

**Example 138:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001481]** Prepared in an analogous manner to **Example 27** using **Intermediate 734** (69 mg, 71 μmol) and lithium hydroxide (5.1 mg, 0.21 mmol) in THF (0.9 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 45-55% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (8.2 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.50 (s, 1H), 7.31 (dd, 1H), 7.04 (dd, 1H), 6.90 – 6.80 (m, 2H), 6.56 (dd, 1H), 5.98 (dd, 1H), 5.51 (dd, 1H), 2.95 – 2.81 (m, 2H), 2.80 – 2.61 (m, 8H), 2.55 (dd, 1H), 2.47 – 2.14 (m, 6H), 2.12 – 1.95 (m, 2H), 1.95 (s, 3H), 1.65 – 0.86 (m, 12H), 0.80 – 0.65 (m, 2H). LCMS (Method 15): 2.01 min, 666.4 $[M+H]^+$.

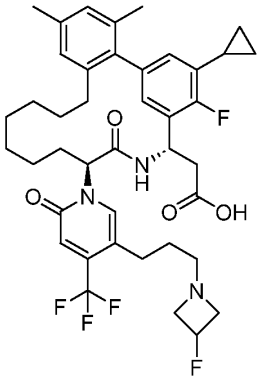
**Example 139:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$,2$^4$-trifluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001482]** Prepared in an analogous manner to **Example 27** using **Intermediate 742** (0.10 g, 0.14 mmol) and lithium hydroxide (9.8 mg, 0.41 mmol) in THF (1.3 mL), MeOH (0.6 mL) and water (0.6 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 45-55% MeCN in 0.1% aqueous ammonia over 20 min) to provide the title compound (38 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.92 (s, 1H), 7.14 (d, 1H), 6.94 (d, 1H),

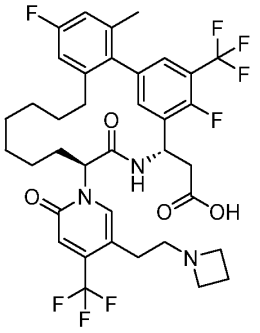
6.89 (s, 1H), 6.83 (dt, 1H), 6.68 (s, 1H), 5.98 (dd, 1H), 5.49 (dd, 1H), 3.25 – 2.86 (m, 4H), 2.72 (s, 6H), 2.62 (dd, 1H), 2.51 – 2.36 (m, 2H), 2.26 – 2.14 (m, 2H), 1.65 – 1.49 (m, 2H), 1.48 – 0.97 (m, 12H), 0.82 – 0.67 (m, 2H). LCMS (Method 15): 1.82 min, 706.3 $[M+H]^+$.

**Example 140:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-2$^4$-fluoro-6-(5-(3-(3-fluoroazetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



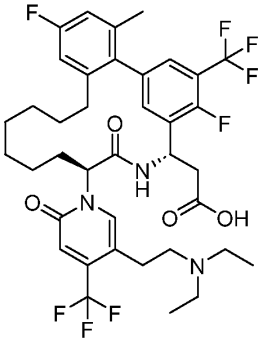
**[001483]** Prepared in an analogous manner to **Example 27** using **Intermediate 744** (17 mg, 22 μmol) and lithium hydroxide (2 mg, 84 μmol) in THF (1.0 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 30-50% MeCN in 0.1% aqueous ammonia over 25 min) to provide the title compound (5 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.91 (s, 1H), 7.08 (dd, 1H), 6.94 (s, 1H), 6.91 (s, 1H), 6.86 (s, 1H), 6.55 (dd, 1H), 5.93 (dd, 1H), 5.47 (dd, 1H), 5.32 – 5.07 (m, 1H), 3.98 – 3.65 (m, 2H), 2.81 – 2.52 (m, 6H), 2.40 – 2.33 (m, 2H), 2.32 (s, 3H), 2.27 – 2.12 (m, 2H), 1.94 (s, 3H), 1.84 – 1.55 (m, 3H), 1.53 – 0.84 (m, 14H), 0.77 – 0.62 (m, 2H). LCMS (Method 15): 1.86 min, 742.3 $[M+H]^+$.

**Example 141:** 2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



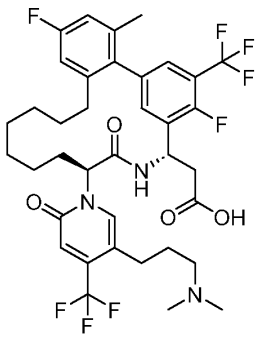
**[001484]** Prepared in an analogous manner to **Example 27** using **Intermediate 749** (85 mg, 0.11 mmol) and lithium hydroxide (7.9 mg, 0.33 mmol) in THF (1.1 mL), MeOH (1.1 mL) and water (0.6 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 45-55% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (39 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.83 (s, 1H), 7.60 (d, 1H), 7.35 (d, 1H), 6.97 – 6.85 (m, 3H), 6.00 (dd, 1H), 5.54 (dd, 1H), 4.19 – 3.53 (br m, 4H), 3.27 – 3.06 (br m, 1H), 2.94 – 2.78 (m, 1H), 2.73 (t, 1H), 2.67 (dd, 1H), 2.56 – 2.32 (m, 4H), 2.32 – 2.17 (m, 2H), 2.00 (s, 3H), 1.66 – 1.47 (m, 2H), 1.46 – 0.92 (m, 10H). LCMS (Method 15): 2.06 min, 742.2 $[M+H]^+$.

**Example 142:** 2-((3*S*,6*S*)-6-(5-(2-(Diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



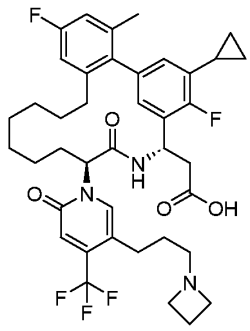
**[001485]** Prepared in an analogous manner to **Example 27** using **Intermediate 752** (0.15 g, 0.16 mmol) and lithium hydroxide (11.7 mg, 0.49 mmol) in THF (2.8 mL), MeOH (1.6 mL) and water (1.6 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 45-55% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (5 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.91 (s, 1H), 7.60 (d, 1H), 7.33 (d, 1H), 6.97 – 6.84 (m, 3H), 5.93 (dd, 1H), 5.50 (dd, 1H), 3.13 – 2.75 (m, 7H), 2.65 (dd, 1H), 2.54 (dd, 1H), 2.49 – 2.39 (m, 1H), 2.37 – 2.15 (m, 2H), 2.00 (s, 3H), 1.71 – 0.91 (m, 18H). LCMS (Method 15): 1.94 min, 758.3 $[M+H]^+$.

**Example 143:** 2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



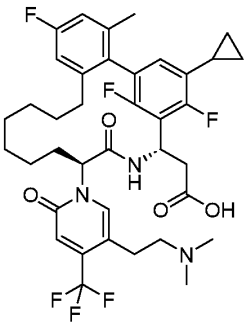
**[001486]** Prepared in an analogous manner to **Example 27** using **Intermediate 754** (76 mg, 98 μmol) and lithium hydroxide (7.1 mg, 0.30 mmol) in THF (1.0 mL), MeOH (1.0 mL) and water (0.6 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 45-55% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (62 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.89 (s, 1H), 7.61 (d, 1H), 7.33 (d, 1H), 6.97 – 6.84 (m, 3H), 5.96 (dd, 1H), 5.51 (dd, 1H), 2.81 – 2.40 (m, 12H), 2.39 – 2.28 (m, 1H), 2.27 – 2.15 (m, 1H), 2.00 (s, 3H), 1.99 – 1.82 (m, 2H), 1.66 – 0.86 (m, 12H). LCMS (Method 15): 2.00 min, 744.3 $[M+H]^+$.

**Example 144:** 2-((3*S*,6*S*)-6-(5-(3-(Azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



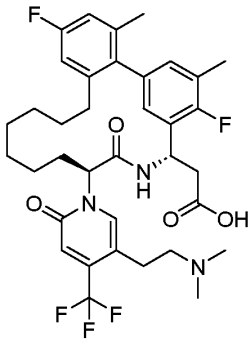
**[001487]** Prepared in an analogous manner to **Example 27** using **Intermediate 758** (76 mg, 0.10 mmol) and lithium hydroxide (12.1 mg, 0.50 mmol) in THF (2.0 mL), MeOH (2.0 mL) and water (1.0 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 55-65% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (24 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.90 (s, 1H), 7.06 (d, 1H), 6.90 – 6.80 (m, 3H), 6.56 (d, 1H), 6.03 (dd, 1H), 5.46 (dd, 1H), 4.04 – 3.60 (m, 4H), 3.08 – 2.76 (m, 2H), 2.75 – 2.65 (m, 1H), 2.64 – 2.52 (m, 2H), 2.47 (dd, 1H), 2.41 – 2.27 (m, 4H), 2.26 – 2.14 (m, 2H), 1.97 (s, 3H), 1.97 – 1.85 (m, 1H), 1.82 – 1.67 (m, 1H), 1.61 – 0.88 (m, 13H), 0.80 – 0.65 (m, 2H). LCMS (Method 15): 2.05 min, 728.3 $[M+H]^+$.

**Example 145:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^2$,2$^4$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001488]** Prepared in an analogous manner to **Example 27** using **Intermediate 772** (0.24 g, 0.26 mmol) and lithium hydroxide (18.7 mg, 0.78 mmol) in THF (6 mL), MeOH (3 mL) and water (3 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 55-65% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (60 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.99 (s, 1H), 6.93 – 6.84 (m, 3H), 6.65 (t, 1H), 5.99 (dd, 1H), 5.42 (dd, 1H), 3.00 – 2.64 (m, 5H), 2.57 (s, 6H), 2.46 – 2.31 (m, 2H), 2.25 – 2.09 (m, 2H), 2.01 (s, 3H), 1.70 – 1.57 (m, 1H), 1.52 – 0.86 (m, 13H), 0.79 – 0.61 (m, 2H). LCMS (Method 15): 1.75 min, 720.3 $[M+H]^+$.

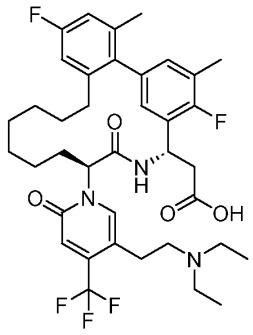
**Example 146:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001489]** Prepared in an analogous manner to **Example 27** using **Intermediate 783** (0.30 g, 0.28 mmol) and lithium hydroxide (10 mg, 0.42 mmol) in THF (6 mL), MeOH (3.2 mL) and water (2 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (78 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.93 (s, 1H), 7.12 (d, 1H), 6.91 – 6.78 (m, 4H), 5.90 (dd, 1H), 5.50 (dd, 1H), 3.05 – 2.79 (m, 4H), 2.62 (dd, 1H), 2.57 (s, 6H), 2.49 (dd,

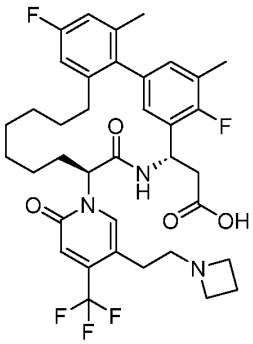
1H), 2.44 – 2.35 (m, 1H), 2.34 (s, 3H), 2.27 – 2.16 (m, 1H), 1.99 (s, 3H), 1.63 – 0.99 (m, 12H). LCMS (Method 15): 1.70 min, 676.3 $[M+H]^+$.

**Example 147:** 2-((3*S*,6*S*)-6-(5-(2-(Diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



Prepared in an analogous manner to **Example 27** using **Intermediate 786** (0.16 g, 0.16 mmol) and lithium hydroxide (5.9 mg, 0.25 mmol) in THF (4 mL), MeOH (1.6 mL) and water (1 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (59 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.91 (s, 1H), 7.08 (d, 1H), 6.94 – 6.79 (m, 4H), 5.96 (dd, 1H), 5.45 (dd, 1H), 3.29 – 2.86 (m, 8H), 2.60 (dd, 1H), 2.44 (dd, 1H), 2.40 – 2.34 (m, 1H), 2.34 (s, 3H), 2.28 – 2.16 (m, 1H), 1.98 (s, 3H), 1.72 – 0.99 (m, 18H). LCMS (Method 15): 1.75 min, 704.3 $[M+H]^+$.

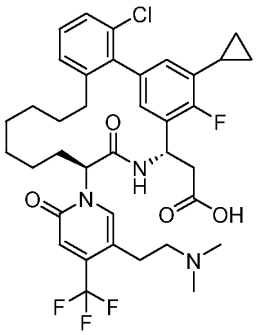
**Example 148:** 2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001490]** Prepared in an analogous manner to **Example 27** using **Intermediate 792** (58 mg, 54 µmol) and lithium hydroxide (2 mg, 81 µmol) in THF (2.6 mL), MeOH (1.1 mL) and water (0.7 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (8.8 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.86 (s, 1H), 7.11 (d, 1H), 6.93 – 6.79 (m, 4H), 5.94

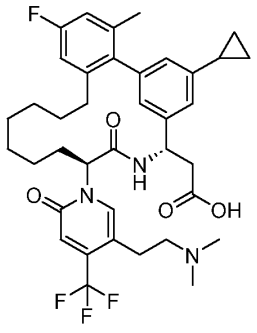
(dd, 1H), 5.52 (dd, 1H), 4.13 – 3.55 (m, 4H), 3.21 – 3.01 (m, 1H), 2.94 – 2.76 (m, 1H), 2.75 – 2.66 (m, 1H), 2.64 (dd, 1H), 2.47 (dd, 1H), 2.43 – 2.18 (m, 8H), 1.99 (s, 3H), 1.65 – 1.48 (m, 2H), 1.47 – 1.01 (m, 10H). LCMS (Method 15): 1.73 min, 688.3 $[M+H]^+$.

**Example 149:** 2-((3*S*,6*S*)-1$^6$-Chloro-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001491]** Prepared in an analogous manner to **Example 27** using **Intermediate 801** (91 mg, 83 µmol) and lithium hydroxide (10 mg, 0.42 mmol) in THF (1.2 mL) and water (0.6 mL) at RT for 5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (7.2 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.93 (s, 1H), 7.34 – 7.24 (m, 3H), 7.14 (dd, 1H), 6.87 (s, 1H), 6.60 (dd, 1H), 5.96 (dd, 1H), 5.50 (dd, 1H), 2.96 – 2.83 (m, 2H), 2.63 (dd, 1H), 2.60 (s, 6H), 2.51 (dd, 1H), 2.49 – 2.34 (m, 3H), 2.26 – 2.15 (m, 2H), 1.65 – 1.48 (m, 2H), 1.46 – 0.86 (m, 12H), 0.79 – 0.64 (m, 2H). LCMS (Method 15): 1.76 min, 704.3 $[M+H]^+$.

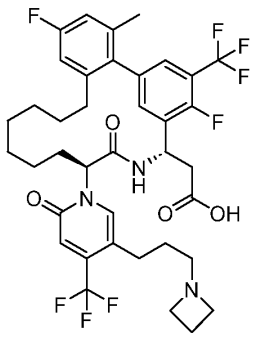
**Example 150:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001492]** Prepared in an analogous manner to **Example 27** using **Intermediate 810** (0.16 g, 0.24 mmol) and lithium hydroxide (3 mg, 0.11 mmol) in THF (1.6 mL), MeOH (0.3 mL) and water (0.8 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm

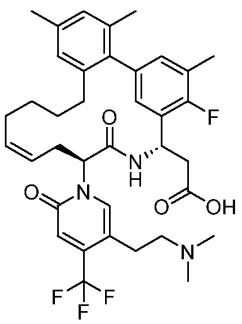
5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (8.4 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.95 (s, 1H), 7.11 (s, 1H), 7.03 (s, 1H), 6.92 – 6.81 (m, 3H), 6.72 (s, 1H), 5.51 (dd, 1H), 5.47 (dd, 1H), 3.22 – 3.02 (m, 1H), 3.02 – 2.86 (m, 2H), 2.72 (s, 6H), 2.58 (dd, 1H), 2.49 (dd, 1H), 2.42 – 2.27 (m, 2H), 2.26 – 2.14 (m, 1H), 1.99 (s, 3H), 1.99 – 1.91 (m, 1H), 1.65 – 1.46 (m, 2H), 1.46 – 1.15 (m, 8H), 1.14 – 0.89 (m, 4H), 0.82 – 0.68 (m, 2H). LCMS (Method 15): 1.85 min, 684.3 $[M+H]^+$.

**Example 151:** 2-((3*S*,6*S*)-6-(5-(3-(Azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



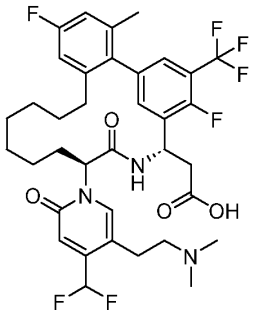
**[001493]** Prepared in an analogous manner to **Example 27** using **Intermediate 814** (45 g, 57 µmol) and lithium hydroxide (4.1 mg, 0.17 mmol) in THF (0.6 mL), MeOH (0.6 mL) and water (0.3 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 50-60% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (33 mg). $^1$H NMR (500 MHz, $CD_3OD$) δ: 7.88 (s, 1H), 7.62 (d, 1H), 7.33 (d, 1H), 6.97 – 6.86 (m, 2H), 6.85 (s, 1H), 5.96 (dd, 1H), 5.50 (dd, 1H), 3.85 – 3.44 (m, 4H), 2.85 – 2.69 (m, 2H), 2.68 – 2.52 (m, 4H), 2.50 – 2.41 (m, 1H), 2.39 – 2.16 (m, 3H), 2.00 (s, 3H), 1.87 – 1.64 (m, 2H), 1.62 – 0.85 (m, 12H). LCMS (Method 15): 2.09 min, 756.3 $[M+H]^+$.

**Example 152:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$,2$^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetic acid



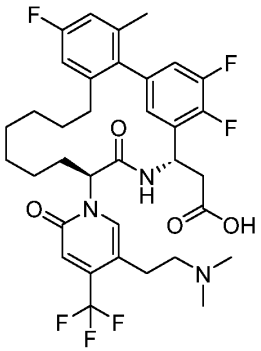
**[001494]** Prepared in an analogous manner to **Example 27** using **Intermediate 562** (0.11 g, 0.11 mmol) and lithium hydroxide (8 mg, 0.34 mmol) in THF (2.3 mL), MeOH (0.9 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (28 mg). $^1$H NMR (500 MHz, $CD_3OD$) δ: 7.80 (s, 1H), 6.98 (dd, 1H), 6.95 – 6.88 (m, 3H), 6.86 (dd, 1H), 5.86 (dd, 1H), 5.63 – 5.53 (m, 1H), 5.43 – 5.29 (m, 2H), 3.26 – 2.87 (m, 4H), 2.86 – 2.77 (m, 1H), 2.72 (s, 6H), 2.65 (dd, 1H), 2.41 – 2.34 (m, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 2.30 – 2.23 (m, 2H), 2.22 – 2.14 (m, 1H), 2.08 – 1.99 (m, 1H), 1.94 (s, 3H), 1.90 – 1.78 (m, 1H), 1.50 – 1.37 (m, 1H), 1.31 – 1.17 (m, 2H), 1.17 – 1.05 (m, 1H). LCMS (Method 22): 1.90 min, 670.3 $[M+H]^+$.

**Example 153:** 2-((3*S*,6*S*)-6-(4-(Difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



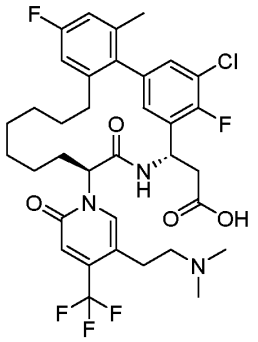
**[001495]** Prepared in an analogous manner to **Example 27** using **Intermediate 820** (0.18 g, 0.25 mmol) and lithium hydroxide (18 mg, 0.74 mmol) in THF (2.7 mL), MeOH (2.6 mL) and water (1.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (54 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.78 (s, 1H), 7.58 (dd, 1H), 7.34 (dd, 1H), 7.03 – 6.70 (m, 4H), 5.99 (dd, 1H), 5.51 (dd, 1H), 3.35 – 3.09 (m, 2H), 3.09 – 2.98 (m, 1H), 2.97 – 2.85 (m, 1H), 2.78 (s, 6H), 2.62 (dd, 1H), 2.51 – 2.40 (m, 1H), 2.31 – 2.17 (m, 2H), 1.99 (s, 3H), 1.64 – 1.46 (m, 2H), 1.44 – 0.86 (m, 10H). LCMS (Method 15): 1.85 min, 712.3 $[M+H]^+$.

**Example 154:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$,2$^5$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



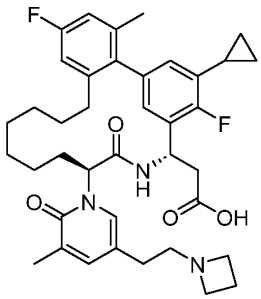
**[001496]** Prepared in an analogous manner to **Example 27** using **Intermediate 832** (61 mg, 71 µmol) and lithium hydroxide (10 mg, 0.42 mmol) in THF (0.5 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 22 min) to provide the title compound (4.3 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.93 (s, 1H), 7.12 (d, 1H), 6.97 – 6.82 (m, 4H), 5.86 (dd, 1H), 5.51 (dd, 1H), 2.95 – 2.51 (m, 5H), 2.46 (s, 6H), 2.46 – 2.37 (m, 2H), 2.30 – 2.16 (m, 1H), 2.02 (s, 3H), 1.70 – 0.98 (m, 12H). LCMS (Method 15): 1.85 min, 678.3 $[M-H]^-$.

**Example 155:** 2-((3*S*,6*S*)-2$^5$-Chloro-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



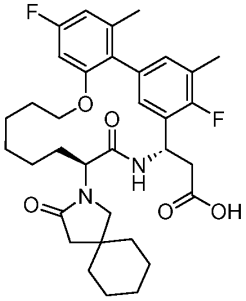
**[001497]** Prepared in an analogous manner to **Example 27** using **Intermediate 843** (0.12 g, 0.14 mmol) and lithium hydroxide (10 mg, 0.43 mmol) in THF (3.4 mL), MeOH (1.7 mL) and water (1.7 mL) at RT for 2.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (26 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.91 (s, 1H), 7.25 (dd, 1H), 7.14 (dd, 1H), 6.93 – 6.83 (m, 3H), 5.89 (dd, 1H), 5.50 (dd, 1H), 3.01 – 2.78 (m, 4H), 2.69 – 2.31 (m, 9H), 2.28 – 2.16 (m, 1H), 2.02 (s, 3H), 1.64 – 0.97 (m, 12H). LCMS (Method 15): 1.84 min, 696.2 $[M+H]^+$.

**Example 156:** 2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001498]** Prepared in an analogous manner to **Example 27** using **Intermediate 849** (30 mg, 38 µmol) and lithium hydroxide (1.4 mg, 58 µmol) in THF (0.8 mL), MeOH (0.3 mL) and water (0.2 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 45-55% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (2 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.50 (s, 1H), 7.33 (s, 1H), 7.08 (dd, 1H), 6.89 – 6.79 (m, 2H), 6.55 (dd, 1H), 5.87 (dd, 1H), 5.58 (dd, 1H), 3.81 – 3.49 (m, 2H), 3.09 – 2.80 (m, 2H), 2.63 (dd, 1H), 2.62 – 2.42 (m, 4H), 2.40 – 2.14 (m, 6H), 2.13 (s, 3H), 1.97 (s, 3H), 1.64 – 0.86 (m, 14H), 0.80 – 0.61 (m, 2H). LCMS (Method 15): 1.95 min, 660.4 $[M+H]^+$.

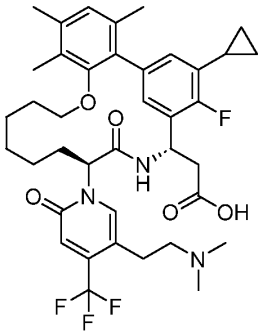
**Example 157:** 2-((10*S*,13*S*)-1$^4$,2$^4$-Difluoro-1$^5$,2$^6$-dimethyl-11-oxo-10-(3-oxo-2-azaspiro[4.5]decan-2-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001499]** A solution of **Intermediate 853** (0.16 g, 0.31 mmol), ethyl 2-(1-formylcyclohexyl)acetate (79 mg, 0.40 mmol, CAS 460711-33-5) and triethylamine (0.21 mL, 1.52 mmol) in EtOAc (6 mL) and IPA (2 mL) was stirred at RT for 18 h. This was added to a stirred solution of sodium borohydride (46 mg, 1.22 mmol) in water (2 mL) and the mixture stirred at RT for 30 min. The mixture was diluted with water and extracted with EtOAc. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in AcOH (3.5 mL) and stirred at 75 °C for 1 h. The mixture was concentrated under reduced pressure then dissolved in THF (2 mL), MeOH (1 mL) and water

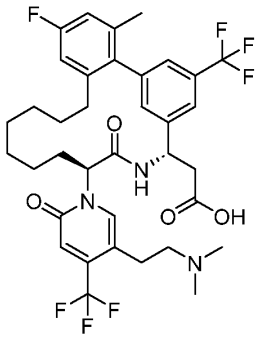
(2 mL) followed by addition of lithium hydroxide (36 mg, 1.52 mmol) and stirred at RT for 1 h. The mixture was concentrated under reduced pressure then purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 25-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (30 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.09 (d, 1H), 6.88 (d, 1H), 6.69 (d, 1H), 6.63 (d, 1H), 5.87 (t, 1H), 4.57 (dd, 1H), 4.04 – 3.84 (m, 2H), 3.55 (d, 1H), 3.29 (d, 1H), 2.73 (d, 2H), 2.31 (m, 3H), 2.30 – 2.20 (m, 2H), 2.00 (s, 3H), 1.92 – 1.79 (m, 1H), 1.65 – 1.10 (m, 16H), 0.96 – 0.85 (m, 3H). LCMS (Method 15): 1.62 min, 597.3 $[M+H]^+$.

**Example 158:** 2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^3$,2$^4$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



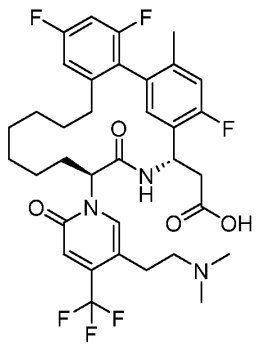
**[001500]** Prepared in an analogous manner to **Example 27** using **Intermediate 862** (0.16 g, 0.12 mmol) and lithium hydroxide (7.2 mg, 0.30 mmol) in THF (4 mL), MeOH (1.5 mL) and water (0.6 mL) at RT for 2.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (33 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.05 (s, 1H), 7.19 (dd, 1H), 6.89 – 6.84 (m, 2H), 6.64 (dd, 1H), 6.01 (dd, 1H), 5.44 (dd, 1H), 3.58 – 3.38 (m, 2H), 3.09 – 2.74 (m, 4H), 2.71 – 2.61 (m, 2H), 2.60 (s, 6H), 2.28 (s, 3H), 2.20 (s, 3H), 2.20 – 2.11 (m, 2H), 1.98 (s, 3H), 1.69 – 1.56 (m, 1H), 1.51 – 0.84 (m, 10H), 0.80 – 0.64 (m, 2H). LCMS (Method 15): 1.83 min, 714.3 $[M+H]^+$.

**Example 159:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



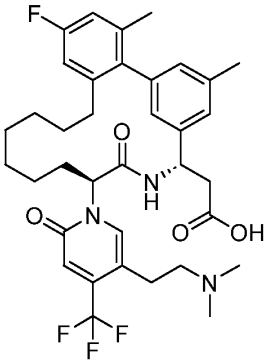
**[001501]** Prepared in an analogous manner to **Example 27** using **Intermediate 875** (0.12 g, 0.12 mmol) and lithium hydroxide (4.4 mg, 0.18 mmol) in THF (5.4 mL), MeOH (2.2 mL) and water (1.4 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (46 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.96 (s, 1H), 7.78 (s, 1H), 7.57 (s, 1H), 7.32 (s, 1H), 6.96 – 6.85 (m, 3H), 5.55 (dd, 1H), 5.50 (dd, 1H), 2.95 – 2.75 (m, 4H), 2.67 (dd, 1H), 2.60 (dd, 1H), 2.53 (s, 6H), 2.51 – 2.30 (m, 2H), 2.26 – 2.11 (m, 1H), 2.01 (s, 3H), 1.67 – 1.53 (m, 1H), 1.52 – 0.89 (m, 10H). LCMS (Method 15): 1.80 min, 712.3 $[M+H]^+$.

**Example 160:** 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$,2$^4$-trifluoro-2$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



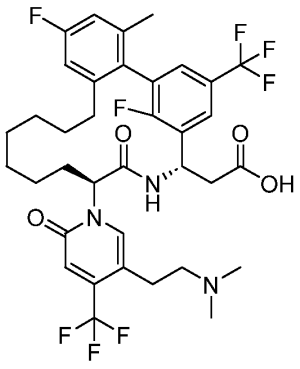
**[001502]** Prepared in an analogous manner to **Example 27** using **Intermediate 888** (0.12 g, 0.13 mmol) and lithium hydroxide (16 mg, 0.66 mmol) in THF (3.1 mL), MeOH (1.5 mL) and water (1.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (46 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.99 (s, 1H), 7.27 (d, 1H), 7.11 (d, 1H), 6.95 (d, 1H), 6.92 – 6.84 (m, 2H), 5.53 (dd, 1H), 5.33 (dd, 1H), 3.14 – 2.73 (m, 4H), 2.71 – 2.53 (m, 2H), 2.53 (s, 6H), 2.52 – 2.35 (m, 1H), 2.28 – 2.16 (m, 1H), 2.15 – 2.06 (m, 1H), 2.05 (s, 3H), 1.70 – 1.52 (m, 1H), 1.51 – 0.86 (m, 10H). LCMS (Method 15): 1.74 min, 680.3 $[M+H]^+$.

**Example 161:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001503]** Prepared in an analogous manner to **Example 27** using **Intermediate 901** (0.14 g, 0.14 mmol) and lithium hydroxide (10 mg, 0.43 mmol) in THF (2.2 mL), MeOH (1.2 mL) and water (1.2 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 45-55% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (30 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.96 (s, 1H), 7.25 (s, 1H), 7.07 (s, 1H), 6.89 – 6.80 (m, 4H), 5.64 – 5.31 (m, 2H), 3.07 – 2.76 (m, 4H), 2.61 (s, 6H), 2.60 – 2.46 (m, 2H), 2.41 (s, 3H), 2.40 – 2.27 (m, 2H), 2.26 – 2.11 (m, 1H), 1.99 (s, 3H), 1.66 – 1.47 (m, 2H), 1.45 – 0.84 (m, 9H). LCMS (Method 21): 3.91 min, 658.3 $[M+H]^+$.

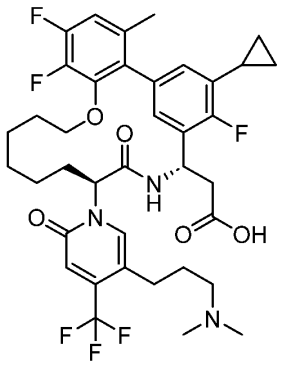
**Example 162:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^2$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001504]** Prepared in an analogous manner to **Example 27** using **Intermediate 914** (0.12 g, 0.15 mmol) and lithium hydroxide (11 mg, 0.46 mmol) in THF (3.6 mL), MeOH (1.8 mL) and water (1.8 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (36 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.10 (s, 1H), 7.85 (dd, 1H), 7.49 (dd, 1H),

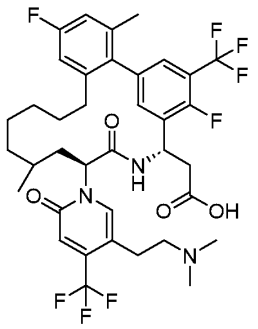
7.00 – 6.86 (m, 3H), 6.04 (dd, 1H), 5.33 (dd, 1H), 3.28 – 3.08 (m, 2H), 3.06 – 2.92 (m, 2H), 2.91 – 2.66 (m, 8H), 2.62 – 2.49 (m, 1H), 2.48 – 2.37 (m, 1H), 2.37 – 2.12 (m, 1H), 2.06 (s, 3H), 1.71 – 1.51 (m, 1H), 1.49 – 0.85 (m, 10H). LCMS (Method 15): 2.02 min, 730.3 $[M+H]^+$.

**Example 163:** 2-((10*S*,13*S*)-$1^5$-Cyclopropyl-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^3$,$2^4$-trifluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid

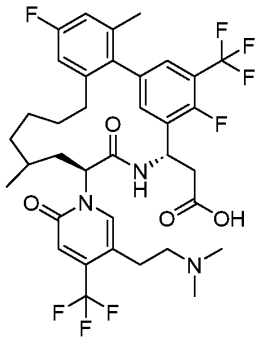


**[001505]** Prepared in an analogous manner to Example **27** using **Intermediate 924** (61 mg, 80 µmol) and lithium hydroxide (3.8 mg, 0.16 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (35 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.01 (s, 1H), 7.15 (dd, 1H), 6.95 (dd, 1H), 6.85 (s, 1H), 6.65 (dd, 1H), 6.03 (dd, 1H), 5.54 (dd, 1H), 3.99 – 3.78 (m, 2H), 2.81 (t, 2H), 2.75 – 2.50 (m, 10H), 2.25 – 2.09 (m, 2H), 2.02 (s, 3H), 2.01 – 1.84 (m, 2H), 1.68 – 1.47 (m, 1H), 1.51 – 0.86 (m, 10H), 0.80 – 0.63 (m, 2H). LCMS (Method 15): 1.83 min, 736.3 $[M+H]^+$.

**Example 164:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,8-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

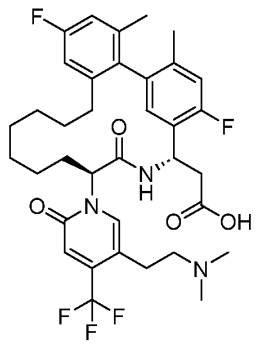


**Example 165:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,8-dimethyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



**[001506]** Prepared in an analogous manner to **Example 27** using **Intermediate 930** (99 mg, 0.13 mmol) and lithium hydroxide (9.2 mg, 0.39 mmol) in THF (1.2 mL), MeOH (0.2 mL) and water (0.6 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-45% MeCN in 0.1% aqueous ammonia over 20 min) to provide **Example 164** (6.9 mg), and **Example 165** (5.9 mg). **Example 164**: $^1$H NMR (400 MHz; $CD_3OD$) δ: 7.87 (s, 1H), 7.61 (dd, 1H), 7.32 (dd, 1H), 6.97 – 6.83 (m, 3H), 5.93 (dd, 1H), 5.61 (dd, 1H), 2.95 – 2.65 (m, 4H), 2.64 (dd, 1H), 2.58 – 2.15 (m, 9H), 2.00 (s, 3H), 1.67 – 1.04 (m, 10H), 1.03 – 0.81 (m, 4H). LCMS (Method 15): 1.88 min, 744.3 $[M+H]^+$. **Example 165**: $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.94 (s, 1H), 7.62 (dd, 1H), 7.34 (dd, 1H), 6.94 – 6.83 (m, 3H), 5.83 (dd, 1H), 5.61 (dd, 1H), 2.84 – 2.51 (m, 6H), 2.49 – 2.26 (m, 7H), 2.25 – 2.08 (m, 1H), 2.02 (s, 3H), 1.56 – 0.88 (m, 9H), 0.85 (d, 3H). LCMS (Method 15): 1.80 min, 730.3 $[M+H]^+$.

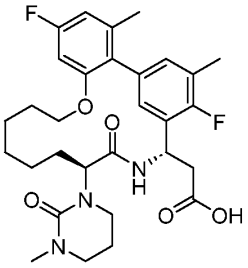
**Example 166:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001507]** Prepared in an analogous manner to **Example 27** using **Intermediate 939** (0.17 g, 0.17 mmol) and lithium hydroxide (21 mg, 0.86 mmol) in THF (4 mL), MeOH (2 mL) and water (2 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5

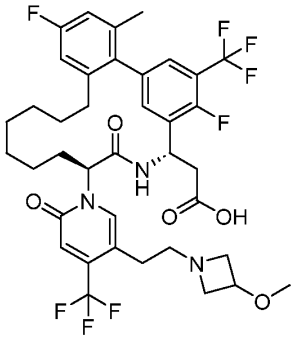
μm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (41 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.98 (s, 1H), 7.17 (dd, 1H), 7.07 (dd, 1H), 6.93 – 6.83 (m, 3H), 5.89 – 5.31 (m, 2H), 2.97 – 2.65 (m, 4H), 2.60 (dd, 1H), 2.52 (dd, 1H), 2.46 (s, 6H), 2.45 – 2.34 (m, 1H), 2.30 – 2.05 (m, 2H), 1.97 (s, 3H), 1.92 (s, 3H), 1.72 – 1.51 (m, 1H), 1.50 – 0.90 (m, 10H). LCMS (Method 15): 1.74 min, 676.3 $[M+H]^+$.

**Example 167:** 2-((10*S*,13*S*)-1$^4$,2$^4$-Difluoro-1$^5$,2$^6$-dimethyl-10-(3-methyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001508]** Prepared in an analogous manner to **Example 27** using **Intermediate 941** (99 mg, 0.16 mmol) and lithium hydroxide (12 mg, 0.49 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (37 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.09 (d, 1H), 6.86 (d, 1H), 6.68 (d, 1H), 6.62 (dd, 1H), 5.81 (dd, 1H), 4.03 – 3.84 (m, 2H), 3.61 – 3.47 (m, 1H), 3.38 – 3.22 (m, 4H), 2.93 (s, 3H), 2.77 – 2.59 (m, 2H), 2.31 (d, 3H), 2.18 – 2.01 (m, 1H), 2.00 (s, 3H), 1.99 – 1.82 (m, 3H), 1.65 – 1.46 (m, 2H), 1.45 – 0.97 (m, 6H). LCMS (Method 15): 1.53 min, 558.3 $[M+H]^+$.

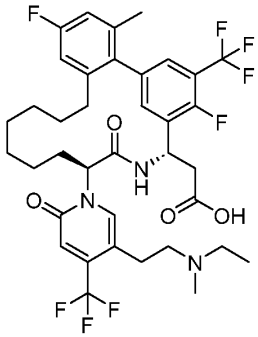
**Example 168:** 2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001509]** Prepared in an analogous manner to **Example 27** using **Intermediate 943** (55 mg, 69 μmol) and lithium hydroxide (2.5 mg, 0.10 mmol) in THF (4.2 mL), MeOH (1.7 mL) and water (1.1 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm,

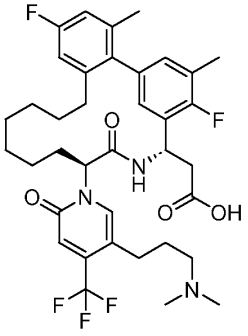
eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (43 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.91 (s, 1H), 7.64 (dd, 1H), 7.32 (dd, 1H), 6.96 – 6.87 (m, 2H), 6.86 (s, 1H), 5.88 (dd, 1H), 5.53 (dd, 1H), 4.17 – 4.06 (m, 1H), 3.93 – 3.62 (m, 2H), 3.31 (s, 3H), 3.27 – 3.07 (m, 2H), 2.98 – 2.53 (m, 6H), 2.52 – 2.30 (m, 2H), 2.29 – 2.16 (m, 1H), 2.01 (s, 3H), 1.69 – 0.86 (m, 11H). LCMS (Method 11): 1.68 min, 772.5 $[M+H]^+$.

**Example 169:** 2-((3*S*,6*S*)-6-(5-(2-(Ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



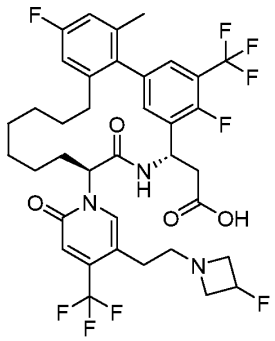
**[001510]** Prepared in an analogous manner to **Example 27** using **Intermediate 948** (0.12 g, 0.15 mmol) and lithium hydroxide (11 mg, 0.45 mmol) in THF (3.6 mL), MeOH (1.8 mL) and water (1.8 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (60 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.91 (s, 1H), 7.60 (dd, 1H), 7.33 (dd, 1H), 6.96 – 6.86 (m, 3H), 5.93 (dd, 1H), 5.50 (dd, 1H), 3.10 – 2.73 (m, 6H), 2.66 (dd, 1H), 2.62 – 2.39 (m, 5H), 2.37 – 2.17 (m, 2H), 2.00 (s, 3H), 1.68 – 0.90 (m, 14H). LCMS (Method 15): 1.68 min, 744.3 $[M+H]^+$.

**Example 170:** 2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



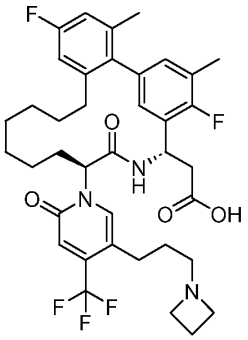
**[001511]** Prepared in an analogous manner to **Example 27** using **Intermediate 957** (0.10 g, 0.13 mmol) and lithium hydroxide (4.5 mg, 0.19 mmol) in THF (3.8 mL), MeOH (1.5 mL) and water (1.0 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (37 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.91 (s, 1H), 7.13 (dd, 1H), 6.98 – 6.75 (m, 4H), 5.91 (dd, 1H), 5.50 (dd, 1H), 2.72 – 2.55 (m, 5H), 2.50 (dd, 1H), 2.48 (s, 6H), 2.48 – 2.35 (m, 3H), 2.34 (s, 3H), 2.27 – 2.14 (m, 1H), 1.99 (s, 3H), 1.97 – 1.78 (m, 2H), 1.68 – 0.99 (m, 10H). LCMS (Method 15): 1.84 min, 690.3 $[M+H]^+$.

**Example 171:** 2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



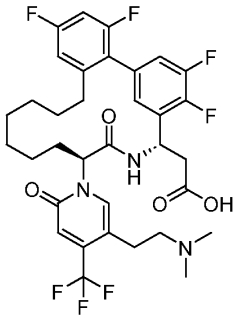
**[001512]** Prepared in an analogous manner to **Example 27** using **Intermediate 959** (55 mg, 70 µmol) and lithium hydroxide (5 mg, 0.21 mmol) in THF (1.7 mL), MeOH (0.8 mL) and water (0.8 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (18 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.91 (s, 1H), 7.13 (dd, 1H), 6.98 – 6.75 (m, 4H), 5.91 (dd, 1H), 5.50 (dd, 1H), 2.72 – 2.55 (m, 5H), 2.50 (dd, 1H), 2.48 (s, 6H), 2.48 – 2.35 (m, 3H), 2.34 (s, 3H), 2.27 – 2.14 (m, 1H), 1.99 (s, 3H), 1.97 – 1.78 (m, 2H), 1.68 – 0.99 (m, 10H). LCMS (Method 15): 1.74 min, 760.2 $[M+H]^+$.

**Example 172:** 2-((3*S*,6*S*)-6-(5-(3-(Azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

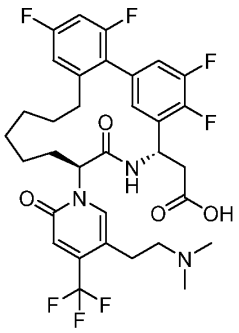


**[001513]** Prepared in an analogous manner to **Example 27** using **Intermediate 963** (41 mg, 57 μmol) and lithium hydroxide (2 mg, 85 μmol) in THF (3.2 mL), MeOH (1.3 mL) and water (0.8 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 45-55% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (23 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.89 (s, 1H), 7.09 (dd, 1H), 6.94 – 6.67 (m, 4H), 6.02 (dd, 1H), 5.46 (dd, 1H), 4.09 – 3.59 (m, 4H), 3.07 – 2.77 (m, 2H), 2.75 – 2.64 (m, 1H), 2.63 – 2.51 (m, 2H), 2.46 (dd, 1H), 2.42 – 2.36 (m, 2H), 2.35 (s, 3H), 2.26 – 2.12 (m, 1H), 1.99 (s, 3H), 1.99 – 1.84 (m, 2H), 1.82 – 1.66 (m, 1H), 1.63 – 0.83 (m, 12H). LCMS (Method 15): 2.02 min, 702.3 $[M+H]^+$.

**Example 173:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$,2$^4$,2$^5$-tetrafluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid

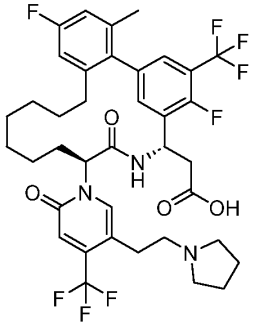


**Example 174:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$,2$^4$,2$^5$-tetrafluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid



**[001514]** Prepared in an analogous manner to **Example 27** using **Intermediate 971** (0.12 g, 0.17 mmol) and lithium hydroxide (8 mg, 0.34 mmol) in THF (1 mL), MeOH (0.4 mL) and water (0.4 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide **Example 173** (35 mg), and **Example 174** (5 mg). **Example 173**: $^1$H NMR (400 MHz; DMSO-$d_6$) δ: 9.44 (br d, 1H), 7.88 (s, 1H), 7.38 – 7.27 (m, 2H), 7.23 – 7.10 (m, 2H), 6.77 (s, 1H), 5.67 (q, 1H), 5.36 (dd, 1H), 3.96 – 2.93 (m, 2H), 2.67 – 2.59 (m, 2H), 2.58 – 2.42 (m, 4H), 2.25 (s, 6H), 2.09 – 1.91 (m, 1H), 1.60 – 0.86 (m, 11H) – OH not observed. LCMS (Method 15): 1.68 min, 684.3 $[M+H]^+$. **Example 174**: $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.12 (s, 1H), 7.19 (d, 1H), 7.14 (dd, 1H), 6.95 (d, 1H), 6.92 (dd, 1H), 6.88 (s, 1H), 5.85 (dd, 1H), 5.44 (dd, 1H), 3.19 – 3.05 (m, 2H), 3.03 – 2.89 (m, 2H), 2.77 (s, 6H), 2.74 – 2.59 (m, 3H), 2.57 – 2.45 (m, 1H), 2.14 – 1.97 (m, 1H), 1.75 – 1.58 (m, 1H), 1.52 – 1.04 (m, 8H). LCMS (Method 15): 1.58 min, 670.3 $[M+H]^+$.

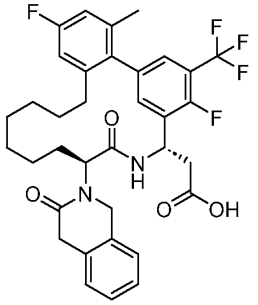
**Example 175:** 2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-1$^6$-methyl-5-oxo-6-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001515]** Prepared in an analogous manner to **Example 27** using **Intermediate 974** (92 mg, 0.12 mmol) and lithium hydroxide (8.4 mg, 0.35 mmol) in THF (2.8 mL), MeOH (1.4 mL) and water (1.4 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (12 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.94 (s, 1H), 7.61 (dd, 1H), 7.33 (dd, 1H), 6.96 – 6.84 (m, 3H), 5.91 (dd, 1H), 5.52 (dd, 1H), 3.21 – 2.75 (m, 8H), 2.64 (dd, 1H), 2.53 (dd,

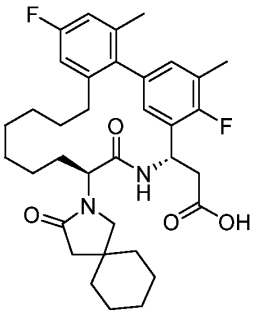
1H), 2.49 – 2.40 (m, 1H), 2.36 – 2.18 (m, 2H), 2.00 (s, 3H), 2.00 – 1.89 (m, 4H), 1.69 – 0.85 (m, 11H). LCMS (Method 15): 1.94 min, 756.3 $[M+H]^+$.

**Example 176:** 2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-$1^6$-methyl-5-oxo-6-(3-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001516]** Prepared in an analogous manner to **Example 27** using **Intermediate 978** (37 mg, 28 µmol) and lithium hydroxide (2 mg, 84 µmol) in THF (1 mL), MeOH (0.2 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-50% MeCN in 0.1% aqueous ammonia over 20 min) to provide the title compound (8 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.61 (dd, 1H), 7.36 – 7.19 (m, 5H), 6.95 – 6.86 (m, 2H), 5.86 (dd, 1H), 5.18 (dd, 1H), 4.62 (d, 1H), 4.55 (d, 1H), 3.73 (d, 1H), 3.61 (d, 1H), 2.71 (dd, 1H), 2.65 (dd, 1H), 2.49 – 2.37 (m, 1H), 2.36 – 2.22 (m, 2H), 1.99 (s, 3H), 1.57 – 0.83 (m, 11H). LCMS (Method 15): 1.79 min, 641.2 $[M-H]^-$.

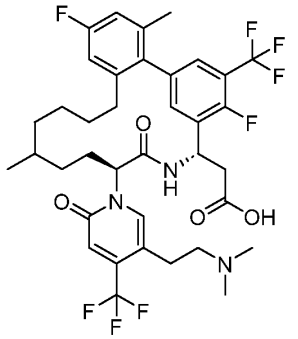
**Example 177:** 2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-$1^6$,$2^5$-dimethyl-5-oxo-6-(3-oxo-2-azaspiro[4.5]decan-2-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



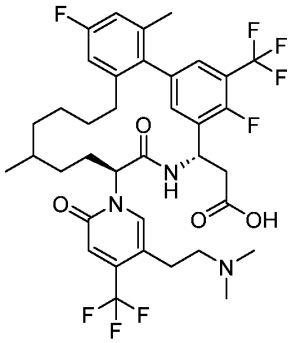
**[001517]** Prepared in an analogous manner to **Example 157** using **Intermediate 982** (0.21 g, 0.40 mmol), ethyl 2-(1-formylcyclohexyl)acetate (0.10 g, 0.52 mmol, CAS 460711-33-5) and triethylamine (0.28 mL, 1.98 mmol) in EtOAc (10 mL) and IPA (3.3 mL) at RT for 18 h. Then sodium borohydride (60 mg, 1.59 mmol) in water (2 mL) at 0 °C for 1 h. Then AcOH (4.5 mL) at 75 °C for 1 h. Finally lithium hydroxide (48 mg, 1.94 mmol) in THF (3.3 mL), MeOH (1.7 mL) and water (3.3 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250

mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (49 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.11 (dd, 1H), 6.96 – 6.78 (m, 3H), 5.82 (dd, 1H), 4.62 (dd, 1H), 3.36 (d, 1H), 3.26 (d, 1H), 2.64 (dd, 1H), 2.59 (dd, 1H), 2.47 – 2.24 (m, 6H), 2.20 (d, 1H), 2.16 – 2.04 (m, 1H), 1.98 (s, 3H), 1.65 – 1.42 (m, 10H), 1.41 – 0.80 (m, 11H). LCMS (Method 15): 1.77 min, 595.3 $[M+H]^+$.

**Example 178:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,9-dimethyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid – Isomer 1



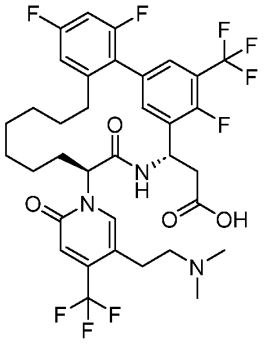
**Example 179:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,9-dimethyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid – Isomer 2



**[001518]** Prepared in an analogous manner to **Example 27** using **Intermediate 992** (35 mg, 45 µmol) and lithium hydroxide (4.3 mg, 0.18 mmol) in THF (0.5 mL), MeOH (0.5 mL) and water (0.2 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-50% MeCN in 0.1% aqueous ammonia over 20 min) to provide **Example 178** (1.2 mg), and **Example 179** (1.9 mg). **Example 178**: $^1$H NMR (500 MHz, $CD_3OD$) δ: 7.92 (s, 1H), 7.60 (dd, 1H), 7.31 (dd, 1H), 6.96 – 6.83 (m, 3H), 5.84 (dd, 1H), 5.40 (dd, 1H), 3.02 – 2.73 (m, 4H), 2.69 (dd, 1H), 2.63 – 2.44 (m, 8H), 2.40 – 2.22 (m, 1H), 2.14 – 2.04 (m, 1H), 2.03 (s, 3H), 1.78 – 1.66 (m, 1H), 1.57 – 0.87 (m, 9H), 0.81 (d, 3H). LCMS (Method 15): 1.85

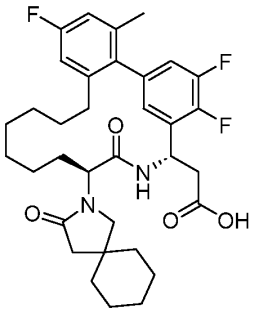
min, 744.3 $[M+H]^+$. **Example 179**: $^1$H NMR (500 MHz, $CD_3OD$) δ: 7.84 (s, 1H), 7.53 (dd, 1H), 7.32 (dd, 1H), 6.95 (dd, 1H), 6.93 – 6.86 (m, 2H), 5.96 (dd, 1H), 5.50 (dd, 1H), 3.26 – 3.03 (m, 2H), 3.03 – 2.87 (m, 2H), 2.72 (s, 6H), 2.64 (dd, 1H), 2.57 – 2.39 (m, 3H), 2.22 – 2.08 (m, 2H), 2.00 (s, 3H), 1.78 – 1.66 (m, 1H), 1.62 – 1.22 (m, 5H), 1.18 – 0.96 (m, 3H), 0.92 (d, 3H). LCMS (Method 15): 1.88 min, 744.3 $[M+H]^+$.

**Example 180:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$,2$^4$-trifluoro-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001519]** Prepared in an analogous manner to **Example 27** using **Intermediate 1000** (0.17 g, 0.11 mmol) and lithium hydroxide (16 mg, 0.66 mmol) in THF (5 mL), MeOH (1 mL) and water (0.5 mL) at RT for 45 min. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (49 mg). $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 9.63 (br s, 1H), 7.90 (s, 1H), 7.85 (d, 1H), 7.58 (d, 1H), 7.28 – 7.12 (m, 2H), 6.77 (s, 1H), 5.66 (q, 1H), 5.37 (dd, 1H), 2.78 – 2.35 (m, 7H), 2.22 (s, 6H), 2.08 – 1.95 (m, 1H), 1.59 – 0.80 (m, 12H) – OH not observed. LCMS (Method 15): 1.77 min, 734.3 $[M+H]^+$.

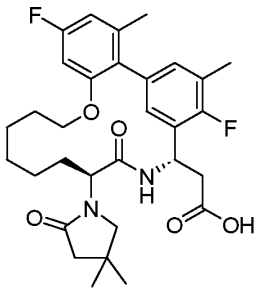
**Example 181:** 2-((3*S*,6*S*)-1$^4$,2$^4$,2$^5$-Trifluoro-1$^6$-methyl-5-oxo-6-(3-oxo-2-azaspiro[4.5]decan-2-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001520]** Prepared in an analogous manner to **Example 157** using **Intermediate 1004** (0.24 g, 0.46 mmol), ethyl 2-(1-formylcyclohexyl)acetate (0.12 g, 0.60 mmol, CAS 460711-33-

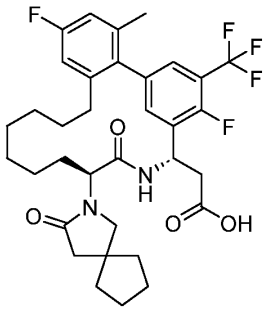
5) and triethylamine (0.32 mL, 2.30 mmol) in EtOAc (9 mL) and IPA (3.1 mL) at RT for 18 h. Then sodium borohydride (70 mg, 1.84 mmol) in water (3.1 mL) at 0 °C for 1 h. Then AcOH (5.3 mL) at 75 °C for 1 h. Finally, lithium hydroxide (55 mg, 2.30 mmol) in THF (3.1 mL), MeOH (1.5 mL) and water (3.1 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 20 min) to provide the title compound (0.13 g). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.09 (d, 1H), 6.96 – 6.81 (m, 3H), 5.81 (t, 1H), 4.61 (dd, 1H), 3.38 (d, 1H), 3.27 (d, 1H), 2.69 (dd, 1H), 2.64 (dd, 1H), 2.46 – 2.35 (m, 2H), 2.32 (d, 1H), 2.20 (d, 1H), 2.17 – 2.04 (m, 1H), 2.01 (s, 3H), 1.66 – 1.41 (m, 11H), 1.40 – 0.98 (m, 10H). LCMS (Method 15): 1.64 min, 599.3 $[M+H]^+$.

**Example 182:** 2-((10*S*,13*S*)-10-(4,4-Dimethyl-2-oxopyrrolidin-1-yl)-1$^4$,2$^4$-difluoro-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



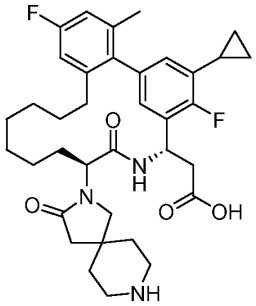
**[001521]** Prepared in an analogous manner to **Example 27** using **Intermediate 1006** (0.11 g, 0.16 mmol) and lithium hydroxide (12 mg, 0.48 mmol) in THF (1 mL), MeOH (1 mL) and water (0.5 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-35% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (51 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.10 (d, 1H), 6.88 (d, 1H), 6.69 (d, 1H), 6.63 (d, 1H), 5.87 (t, 1H), 4.58 (dd, 1H), 4.03 – 3.83 (m, 2H), 3.50 (d, 1H), 3.24 (d, 1H), 2.72 (d, 2H), 2.31 (s, 3H), 2.26 (d, 1H), 2.19 (d, 1H), 2.00 (s, 3H), 1.91 – 1.77 (m, 1H), 1.63 – 1.46 (m, 2H), 1.46 – 0.91 (m, 7H), 1.19 (s, 3H), 1.14 (s, 3H). LCMS (Method 15): 1.39 min, 557.2 $[M+H]^+$.

**Example 183:** 2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-1$^6$-methyl-5-oxo-6-(3-oxo-2-azaspiro[4.4]nonan-2-yl)-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



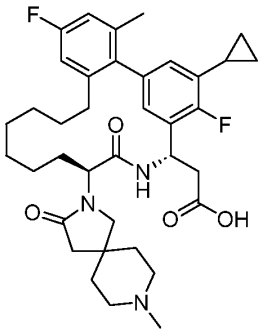
**[001522]** Prepared in an analogous manner to **Example 27** using **Intermediate 1008** (88 mg, 0.13 mmol) and lithium hydroxide (16 mg, 0.66 mmol) in THF (2 mL), MeOH (1 mL) and water (2 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (1.8 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.60 (dd, 1H), 7.29 (dd, 1H), 6.95 – 6.84 (m, 2H), 5.85 (t, 1H), 4.63 (dd, 1H), 3.43 (d, 1H), 3.32 (d, 1H), 2.69 (dd, 1H), 2.63 (dd, 1H), 2.48 – 2.27 (m, 4H), 2.18 – 2.03 (m, 1H), 2.00 (s, 3H), 1.82 – 1.54 (m, 6H), 1.52 – 0.84 (m, 13H). LCMS (Method 15): 1.76 min, 635.3 $[M+H]^+$.

**Example 184:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-6-(3-oxo-2,8-diazaspiro[4.5]decan-2-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



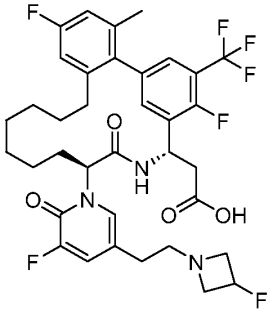
**[001523]** Prepared in an analogous manner to **Example 27** using **Intermediate 1016** (40 mg, 62 µmol) and lithium hydroxide (7.3 mg, 0.31 mmol) in THF (1 mL), MeOH (0.5 mL) and water (1 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (25 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.04 (dd, 1H), 6.88 – 6.78 (m, 2H), 6.52 (dd, 1H), 5.87 (dd, 1H), 4.63 (dd, 1H), 3.46 (d, 1H), 3.39 – 3.27 (m, 1H), 3.10 – 2.85 (m, 4H), 2.61 (dd, 1H), 2.53 (dd, 1H), 2.43 (d, 1H), 2.38 – 2.27 (m, 2H), 2.25 – 2.04 (m, 2H), 1.96 (s, 3H), 1.87 – 1.60 (m, 4H), 1.55 – 0.85 (m, 14H), 0.79 – 0.62 (m, 2H). LCMS (Method 15): 1.78 min, 622.3 $[M+H]^+$.

**Example 185:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-6-(8-methyl-3-oxo-2,8-diazaspiro[4.5]decan-2-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001524]** Prepared in an analogous manner to **Example 27** using **Intermediate 1017** (50 mg, 75 µmol) and lithium hydroxide (9 mg, 0.38 mmol) in THF (1 mL), MeOH (0.5 mL) and water (1 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (33 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.05 (dd, 1H), 6.88 – 6.78 (m, 2H), 6.52 (dd, 1H), 5.86 (dd, 1H), 4.63 (dd, 1H), 3.45 (d, 1H), 3.41 – 3.27 (m, 1H), 2.89 – 2.64 (m, 4H), 2.62 (dd, 1H), 2.54 (dd, 1H), 2.50 (s, 3H), 2.46 – 2.26 (m, 3H), 2.23 – 2.05 (m, 2H), 1.96 (s, 3H), 1.92 – 1.65 (m, 4H), 1.57 – 0.85 (m, 14H), 0.79 – 0.62 (m, 2H). LCMS (Method 15): 1.70 min, 636.3 $[M+H]^+$.

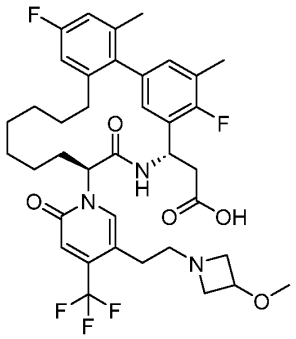
**Example 186:** 2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001525]** Prepared in an analogous manner to **Example 27** using **Intermediate 1022** (37 mg, 23 µmol) and lithium hydroxide (3.2 mg, 0.14 mmol) in THF (1 mL), MeOH (0.2 mL) and water (0.1 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (6.4 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.64 (dd, 1H), 7.53 (s, 1H), 7.34 (dd, 1H), 7.31 (dd, 1H), 6.96 – 6.85 (m, 2H), 5.85 (dd, 1H), 5.56 (dd, 1H), 5.28 – 5.05 (m, 1H), 3.83 –

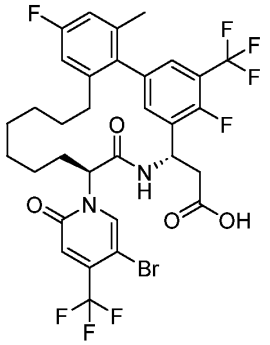
3.65 (m, 2H), 3.47 – 3.20 (m, 2H), 2.91 – 2.74 (m, 2H), 2.68 (dd, 1H), 2.59 (dd, 1H), 2.58 – 2.49 (m, 2H), 2.48 – 2.30 (m, 2H), 2.29 – 2.15 (m, 1H), 2.01 (s, 3H), 1.68 – 0.85 (m, 11H). LCMS (Method 15): 1.85 min, 710.3 $[M+H]^+$.

**Example 187:** 2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



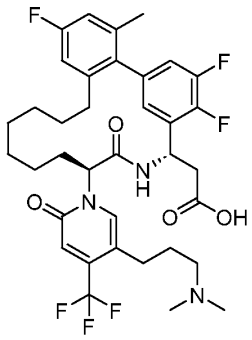
**[001526]** Prepared in an analogous manner to Example **27** using **Intermediate 1025** (28 mg, 38 µmol) and lithium hydroxide (2.7 mg, 0.11 mmol) in THF (0.5 mL), MeOH (0.5 mL) and water (0.2 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (14 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.84 (s, 1H), 7.09 (d, 1H), 6.92 – 6.80 (m, 4H), 5.96 (dd, 1H), 5.52 (dd, 1H), 4.40 – 4.08 (m, 3H), 3.92 – 3.66 (m, 2H), 3.37 (s, 3H), 3.33 – 3.20 (m, 2H), 2.99 – 2.86 (m, 1H), 2.83 – 2.70 (m, 1H), 2.63 (dd, 1H), 2.43 (dd, 1H), 2.41 – 2.35 (m, 1H), 2.35 (s, 3H), 2.34 – 2.18 (m, 2H), 1.99 (s, 3H), 1.66 – 1.48 (m, 2H), 1.47 – 0.90 (m, 9H). LCMS (Method 15): 1.76 min, 718.3 $[M+H]^+$.

**Example 188:** 2-((3*S*,6*S*)-6-(5-Bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



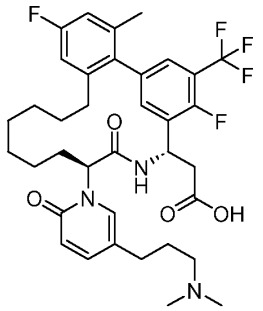
**[001527]** Prepared in an analogous manner to **Example 27** using **Intermediate 1026** (28 mg, 28 μmol) and lithium hydroxide (2 mg, 84 μmol) in THF (0.5 mL), MeOH (0.3 mL) and water (0.3 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (5 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.24 (s, 1H), 7.65 (dd, 1H), 7.32 (dd, 1H), 6.96 (s, 1H), 6.94 – 6.86 (m, 2H), 5.87 (dd, 1H), 5.48 (dd, 1H), 2.69 (dd, 1H), 2.63 (dd, 1H), 2.52 – 2.32 (m, 2H), 2.25 – 2.11 (m, 1H), 2.02 (s, 3H), 1.73 – 0.83 (m, 11H). LCMS (Method 15): 1.93 min, 739.2 $[M+H]^+$.

**Example 189:** 2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$,2$^5$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



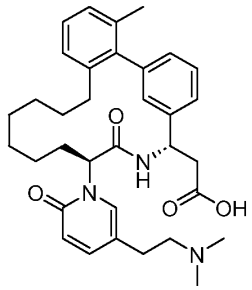
**[001528]** Prepared in an analogous manner to **Example 27** using **Intermediate 1030** (74 mg, 95 μmol) and lithium hydroxide (11 mg, 0.48 mmol) in THF (1.6 mL), MeOH (0.8 mL) and water (0.8 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (46 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.89 (s, 1H), 7.09 (d, 1H), 6.99 – 6.82 (m, 4H), 5.96 (dd, 1H), 5.48 (dd, 1H), 2.84 – 2.59 (m, 5H), 2.59 (s, 6H), 2.58 – 2.46 (m, 1H), 2.45 – 2.34 (m, 2H), 2.28 – 2.15 (m, 1H), 2.01 (s, 3H), 2.00 – 1.83 (m, 2H), 1.68 – 0.86 (m, 11H). LCMS (Method 15): 1.97 min, 694.3 $[M+H]^+$.

**Example 190:** 2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



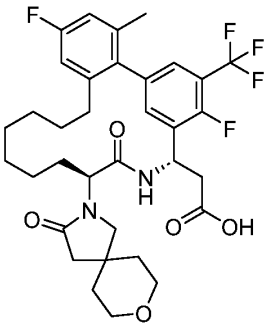
**[001529]** Prepared in an analogous manner to **Example 27** using **Intermediate 1034** (71 mg, 87 μmol) and lithium hydroxide (10 mg, 0.43 mmol) in THF (1.4 mL), MeOH (0.7 mL) and water (0.7 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (40 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.63 (d, 1H), 7.61 (dd, 1H), 7.43 (dd, 1H), 7.32 (dd, 1H), 6.97 – 6.86 (m, 2H), 6.54 (d, 1H), 5.94 (dd, 1H), 5.51 (dd, 1H), 2.71 (t, 2H), 2.66 – 2.57 (m, 2H), 2.57 (s, 6H), 2.54 (dd, 1H), 2.50 – 2.14 (m, 4H), 1.99 (s, 3H), 1.99 – 1.80 (m, 2H), 1.64 – 0.86 (m, 11H). LCMS (Method 15): 1.89 min, 676.3 $[M+H]^+$.

**Example 191:** 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



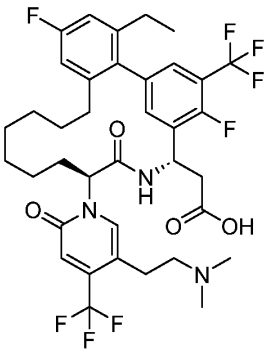
**[001530]** Prepared in an analogous manner to **Example 27** using **Intermediate 1042** (85 mg, 0.15 mmol) and lithium hydroxide (11 mg, 0.45 mmol) in THF (1.0 mL), MeOH (0.3 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (31 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.73 (d, 1H), 7.49 (dd, 1H), 7.46 – 7.36 (m, 2H), 7.29 (s, 1H), 7.21 – 6.97 (m, 4H), 6.56 (d, 1H), 5.67 – 5.31 (m, 2H), 3.13 – 2.91 (m, 2H), 2.88 – 2.70 (m, 2H), 2.64 (s, 6H), 2.59 (dd, 1H), 2.50 (dd, 1H), 2.43 – 2.28 (m, 2H), 2.28 – 2.16 (m, 1H), 1.98 (s, 3H), 1.61 – 1.46 (m, 2H), 1.46 – 0.84 (m, 9H). LCMS (Method 15): 1.61 min, 558.3 $[M+H]^+$.

**Example 192:** 2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-1$^6$-methyl-5-oxo-6-(3-oxo-8-oxa-2-azaspiro[4.5]decan-2-yl)-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



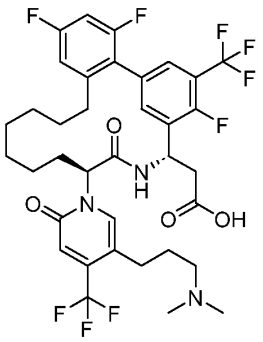
**[001531]** Prepared in an analogous manner to **Example 27** using **Intermediate 1045** (0.12 g, 0.18 mmol) and lithium hydroxide (13 mg, 0.54 mmol) in THF (1.0 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (60 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.60 (dd, 1H), 7.33 (dd, 1H), 6.95 – 6.85 (m, 2H), 5.88 (dd, 1H), 4.63 (dd, 1H), 3.78 – 3.63 (m, 4H), 3.46 (d, 1H), 3.35 (d, 1H), 2.76 – 2.64 (m, 2H), 2.49 – 2.25 (m, 4H), 2.19 – 2.05 (m, 1H), 1.99 (s, 3H), 1.79 – 1.55 (m, 4H), 1.53 – 0.78 (m, 11H). LCMS (Method 15): 1.71 min, 651.3 $[M+H]^+$.

**Example 193:** 2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-ethyl-1$^4$,2$^4$-difluoro-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



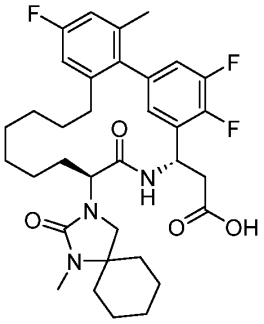
**[001532]** Prepared in an analogous manner to **Example 27** using **Intermediate 1058** (0.12 g, 0.11 mmol) and lithium hydroxide (8 mg, 0.33 mmol) in THF (1.9 mL), MeOH (1.1 mL) and water (1.1 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (39 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.90 (s, 1H), 7.61 (d, 1H), 7.35 (d, 1H), 6.98 – 6.82 (m, 3H), 5.97 (dd, 1H), 5.50 (dd, 1H), 3.11 – 2.72 (m, 4H), 2.65 (dd, 1H), 2.63 (s, 6H), 2.52 (dd, 1H), 2.48 – 2.38 (m, 1H), 2.35 – 2.17 (m, 4H), 1.68 – 1.14 (m, 10H), 1.53 – 1.03 (m, 1H), 1.03 (t, 3H). LCMS (Method 15): 1.97 min, 744.3 $[M+H]^+$.

**Example 194:** 2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$-trifluoro-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001533]** Prepared in an analogous manner to **Example 27** using **Intermediate 1062** (77 mg, 0.10 mmol) and lithium hydroxide (7.1 mg, 0.30 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 45 min. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 30 min) to provide the title compound (18 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.88 (s, 1H), 7.66 (d, 1H), 7.48 (d, 1H), 7.02 (d, 1H), 6.92 (dt, 1H), 6.87 (s, 1H), 6.08 (dd, 1H), 5.46 (dd, 1H), 2.95 (t, 2H), 2.76 (s, 6H), 2.76 – 2.67 (m, 2H), 2.65 – 2.36 (m, 5H), 2.28 – 1.91 (m, 3H), 1.72 – 0.87 (m, 10H). LCMS (Method 15): 2.09 min, 748.3 $[M+H]^+$.

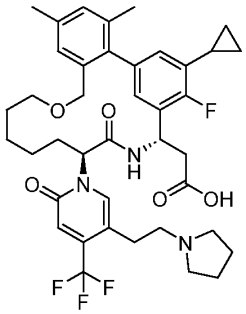
**Example 195:** 2-((3*S*,6*S*)-$1^4$,$2^4$,$2^5$-Trifluoro-$1^6$-methyl-6-(1-methyl-2-oxo-1,3-diazaspiro[4.5]decan-3-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001534]** Prepared in an analogous manner to **Example 27** using **Intermediate 1067** (15 mg, 23 µmol) and lithium hydroxide (2.7 mg, 0.11 mmol) in THF (0.2 mL), MeOH (0.1 mL) and water (0.2 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (2.8 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.09 (d, 1H), 6.94 – 6.81 (m, 3H), 5.82 (t, 1H), 4.38 (dd, 1H), 3.43 (d, 1H), 3.28 (d, 1H), 2.71 (s, 3H), 2.69 (dd, 1H), 2.64 (dd, 1H), 2.47

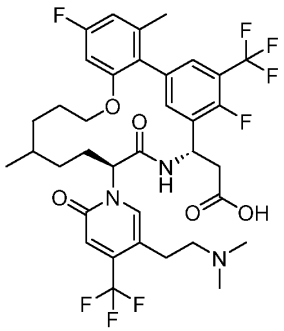
– 2.31 (m, 2H), 2.15 – 2.02 (m, 1H), 2.01 (s, 3H), 1.87 – 1.58 (m, 6H), 1.55 – 0.84 (m, 15H). LCMS (Method 15): 1.69 min, 614.3 $[M+H]^+$.

**Example 196:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-6-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-12-oxa-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001535]** Prepared in an analogous manner to **Example 27** using **Intermediate 1076** (0.35 g, 0.47 mmol) and lithium hydroxide (35 mg, 1.46 mmol) in THF (4 mL), MeOH (2 mL) and water (1.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-40% MeCN in 0.1% aqueous ammonia over 18 min) to provide the title compound (3.4 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.01 (s, 1H), 7.19 – 7.00 (m, 3H), 6.92 (s, 1H), 6.57 (dd, 1H), 6.01 – 5.71 (m, 1H), 5.27 (dd, 1H), 4.19 – 4.07 (m, 2H), 3.50 – 2.95 (m, 6H), 2.88 (dd, 1H), 2.58 (dd, 1H), 2.36 (s, 3H), 2.26 – 2.10 (m, 2H), 2.10 – 1.96 (m, 5H), 1.95 (s, 3H), 1.77 – 1.12 (m, 9H), 1.08 – 0.96 (m, 2H), 0.96 – 0.82 (m, 1H), 0.79 – 0.63 (m, 2H). LCMS (Method 15): 2.01 min, 726.3 $[M+H]^+$.

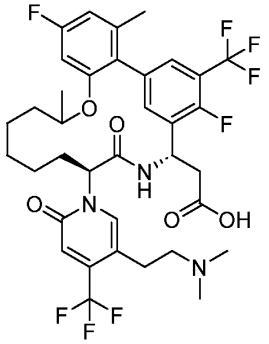
**Example 197:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-2$^6$,7-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



**[001536]** Prepared in an analogous manner to **Example 27** using **Intermediate 1083** (52 mg, 46 µmol) and lithium hydroxide (5.5 mg, 0.23 mmol) in THF (1 mL), MeOH (0.5 mL) and water (1.0 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 45-55% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title

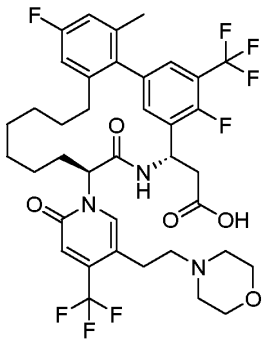
compound (2.5 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.01 (s, 1H), 7.19 – 7.00 (m, 3H), 6.92 (s, 1H), 6.57 (dd, 1H), 6.01 – 5.71 (m, 1H), 5.27 (dd, 1H), 4.19 – 4.07 (m, 2H), 3.50 – 2.95 (m, 6H), 2.88 (dd, 1H), 2.58 (dd, 1H), 2.36 (s, 3H), 2.26 – 2.10 (m, 2H), 2.10 – 1.96 (m, 5H), 1.95 (s, 3H), 1.77 – 1.12 (m, 9H), 1.08 – 0.96 (m, 2H), 0.96 – 0.82 (m, 1H), 0.79 – 0.63 (m, 2H). LCMS (Method 15): 1.80 min, 746.2 $[M+H]^+$.

**Example 198:** 2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-2$^6$,4-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid



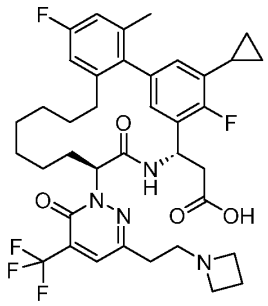
**[001537]** Prepared in an analogous manner to **Example 27** using **Intermediate 1090** (0.10 g, 88 μmol) and lithium hydroxide (11 mg, 0.44 mmol) in THF (1.5 mL), MeOH (0.8 mL) and water (1.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 45-55% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (11 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.01 (s, 1H), 7.19 – 7.00 (m, 3H), 6.92 (s, 1H), 6.57 (dd, 1H), 6.01 – 5.71 (m, 1H), 5.27 (dd, 1H), 4.19 – 4.07 (m, 2H), 3.50 – 2.95 (m, 6H), 2.88 (dd, 1H), 2.58 (dd, 1H), 2.36 (s, 3H), 2.26 – 2.10 (m, 2H), 2.10 – 1.96 (m, 5H), 1.95 (s, 3H), 1.77 – 1.12 (m, 9H), 1.08 – 0.96 (m, 2H), 0.96 – 0.82 (m, 1H), 0.79 – 0.63 (m, 2H). LCMS (Method 15): 1.62 min, 746.2 $[M+H]^+$.

**Example 199:** 2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-1$^6$-methyl-6-(5-(2-morpholinoethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



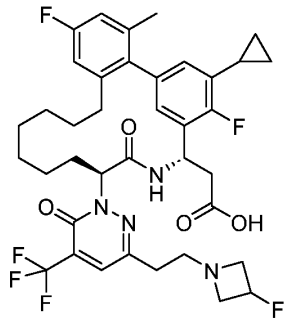
**[001538]** Prepared in an analogous manner to **Example 27** using **Intermediate 1095** (0.11 g, 0.14 mmol) and lithium hydroxide (10 mg, 0.42 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 45 min. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (60 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.01 (s, 1H), 7.61 (dd, 1H), 7.35 (dd, 1H), 6.97 – 6.82 (m, 3H), 5.91 (dd, 1H), 5.50 (dd, 1H), 3.80 (t, 4H), 2.91 – 2.57 (m, 10H), 2.51 – 2.41 (m, 1H), 2.39 – 2.19 (m, 2H), 2.01 (s, 3H), 1.66 – 1.54 (m, 1H), 1.54 – 0.86 (m, 10H). LCMS (Method 15): 1.73 min, 772.3 $[M+H]^+$.

**Example 200:** 2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



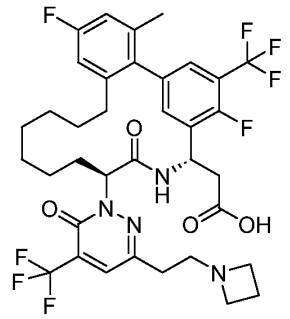
**[001539]** Prepared in an analogous manner to **Example 27** using **Intermediate 1101** (70 mg, 57 µmol) and lithium hydroxide (4.1 mg, 0.17 mmol) in THF (1 mL), MeOH (1 mL) and water (0.5 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-55% MeCN in 0.1% aqueous ammonia over 20 min) to provide the title compound (12 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.82 (s, 1H), 7.05 (dd, 1H), 6.90 – 6.78 (m, 2H), 6.56 (dd, 1H), 5.85 (dd, 1H), 5.56 (dd, 1H), 4.36 – 3.70 (m, 4H), 3.63 – 3.18 (m, 2H), 3.12 – 2.83 (m, 2H), 2.63 (dd, 1H), 2.56 – 2.23 (m, 5H), 2.23 – 2.11 (m, 1H), 1.97 (s, 3H), 1.69 – 1.47 (m, 2H), 1.46 – 0.87 (m, 12H), 0.80 – 0.64 (m, 2H). LCMS (Method 15): 1.96 min, 715.3 $[M+H]^+$.

**Example 201:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



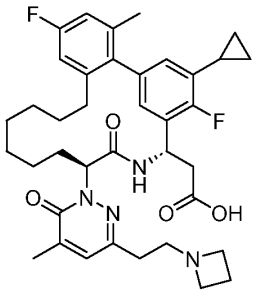
**[001540]** Prepared in an analogous manner to **Example 27** using Intermediate **1103** (58 mg, 76 µmol) and lithium hydroxide (3.7 mg, 0.15 mmol) in THF (0.5 mL), MeOH (0.3 mL) and water (0.3 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 45-55% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (11 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.82 (s, 1H), 7.10 (dd, 1H), 6.90 – 6.78 (m, 2H), 6.53 (dd, 1H), 5.80 (dd, 1H), 5.45 (dd, 1H), 5.33 – 5.11 (m, 1H), 4.01 – 3.85 (m, 2H), 3.65 – 3.49 (m, 2H), 3.11 (t, 2H), 2.96 – 2.80 (m, 2H), 2.69 (dd, 1H), 2.55 (dd, 1H), 2.41 – 2.26 (m, 3H), 2.22 – 2.12 (m, 1H), 1.98 (s, 3H), 1.76 – 1.65 (m, 1H), 1.57 – 0.87 (m, 12H), 0.78 – 0.63 (m, 2H). LCMS (Method 15): 1.79 min, 733.3 $[M+H]^+$.

**Example 202:** 2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



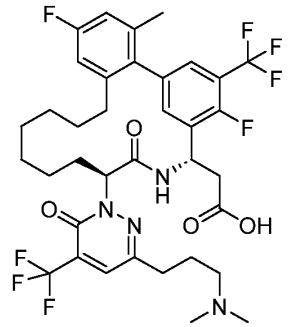
**[001541]** Prepared in an analogous manner to **Example 27** using **Intermediate 1108** (10 mg, 13 µmol) and lithium hydroxide (0.6 mg, 26 µmol) in THF (0.3 mL), MeOH (0.1 mL) and water (0.1 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 50-60% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (4.5 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.82 (s, 1H), 7.63 (d, 1H), 7.30 (d, 1H), 6.96 – 6.83 (m, 2H), 5.82 (dd, 1H), 5.58 – 5.34 (m, 1H), 3.91 – 3.42 (m, 4H), 3.30 – 3.00 (m, 2H), 2.98 – 2.77 (m, 2H), 2.71 (dd, 1H), 2.59 (dd, 1H), 2.51 – 2.15 (m, 5H), 2.00 (s, 3H), 1.82 – 1.61 (m, 1H), 1.57 – 0.88 (m, 10H). LCMS (Method 15): 1.96 min, 743.3 $[M+H]^+$.

**Example 203:** 2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001542]** Prepared in an analogous manner to **Example 27** using **Intermediate 1115** (36 mg, 53 µmol) and lithium hydroxide (3.8 mg, 0.16 mmol) in THF (0.5 mL), MeOH (0.1 mL) and water (0.2 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 45-55% MeCN in 0.1% aqueous ammonia over 25 min) to provide the title compound (8.2 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.25 (q, 1H), 7.08 (dd, 1H), 6.89 – 6.78 (m, 2H), 6.54 (dd, 1H), 5.81 (dd, 1H), 5.50 (dd, 1H), 4.10 – 3.48 (br m, 4H), 2.91 – 2.71 (m, 2H), 2.64 (dd, 1H), 2.51 (dd, 1H), 2.56 – 2.28 (m, 5H), 2.19 (d, 3H), 2.18 – 2.11 (m, 2H), 1.97 (s, 3H), 1.68 – 1.47 (m, 2H), 1.45 – 1.06 (m, 10H), 1.05 – 0.93 (m, 2H), 0.78 – 0.65 (m, 2H). LCMS (Method 15): 1.97 min, 661.4 $[M+H]^+$.

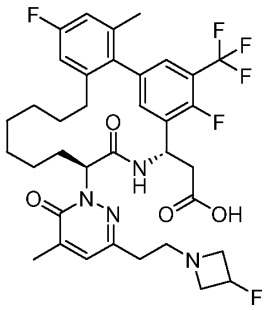
**Example 204:** 2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001543]** Prepared in an analogous manner to **Example 27** using **Intermediate 1117** (67 mg, 87 µmol) and lithium hydroxide (6.2 mg, 0.26 mmol) in THF (0.9 mL), MeOH (0.9 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 45-55% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (32 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.80 (s, 1H), 7.60 (d, 1H), 7.31 (d, 1H), 6.97 – 6.83 (m, 2H), 5.84 (dd, 1H), 5.44 (dd, 1H), 2.98 – 2.73 (m, 4H), 2.72 – 2.38 (m, 9H),

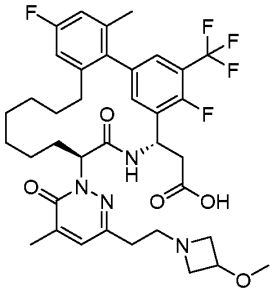
2.37 – 2.24 (m, 2H), 2.18 – 2.01 (m, 2H), 2.00 (s, 3H), 1.78 – 1.59 (m, 1H), 1.55 – 0.88 (m, 10H). LCMS (Method 15): 1.90 min, 745.3 $[M+H]^+$.

**Example 205:** 2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001544]** Prepared in an analogous manner to **Example 27** using **Intermediate 1122** (80 mg, 0.11 mmol) and lithium hydroxide (7.8 mg, 0.33 mmol) in THF (1.1 mL), MeOH (1 mL) and water (0.6 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (37 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.63 (dd, 1H), 7.30 (dd, 1H), 7.27 (s, 1H), 6.96 – 6.84 (m, 2H), 5.78 (dd, 1H), 5.46 (dd, 1H), 5.35 – 5.11 (m, 1H), 4.09 – 3.81 (m, 2H), 3.73 – 3.48 (m, 2H), 3.21 – 2.99 (m, 2H), 2.86 – 2.73 (m, 2H), 2.70 (dd, 1H), 2.57 (dd, 1H), 2.50 – 2.24 (m, 3H), 2.20 (s, 3H), 2.00 (s, 3H), 1.76 – 1.58 (m, 1H), 1.57 – 1.02 (m, 10H). LCMS (Method 15): 1.63 min, 707.2 $[M+H]^+$.

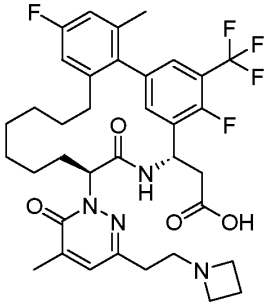
**Example 206:** 2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001545]** Prepared in an analogous manner to **Example 27** using **Intermediate 1124** (99 mg, 0.13 mmol) and lithium hydroxide (9.5 mg, 0.40 mmol) in THF (1.3 mL), MeOH (1.3 mL) and water (0.8 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (39 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.63 (dd, 1H), 7.30 (dd, 1H), 7.26 (s, 1H),

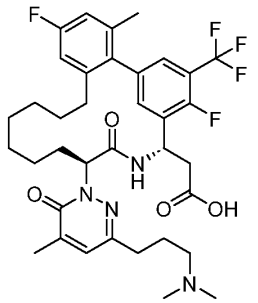
6.96 – 6.84 (m, 2H), 5.78 (dd, 1H), 5.47 (dd, 1H), 4.28 – 4.12 (m, 1H), 4.09 – 3.76 (m, 2H), 3.53 – 3.35 (m, 2H), 3.33 (s, 3H), 3.20 – 2.98 (m, 2H), 2.87 – 2.71 (m, 2H), 2.69 (dd, 1H), 2.56 (dd, 1H), 2.50 – 2.24 (m, 3H), 2.19 (s, 3H), 2.00 (s, 3H), 1.76 – 1.58 (m, 1H), 1.57 – 1.00 (m, 10H). LCMS (Method 15): 1.71 min, 719.3 $[M+H]^+$.

**Example 207:** 2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001546]** Prepared in an analogous manner to **Example 27** using **Intermediate 1126** (68 mg, 0.10 mmol) and lithium hydroxide (6.8 mg, 0.29 mmol) in THF (0.9 mL), MeOH (0.9 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (25 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.60 (dd, 1H), 7.33 (dd, 1H), 7.26 (s, 1H), 6.98 – 6.85 (m, 2H), 5.87 (dd, 1H), 5.57 (dd, 1H), 4.41 – 3.78 (br m, 4H), 3.71 – 3.31 (br m, 2H), 3.02 – 2.77 (m, 2H), 2.63 (dd, 1H), 2.58 – 2.34 (m, 5H), 2.33 – 2.20 (m, 1H), 2.20 (s, 3H), 2.00 (s, 3H), 1.70 – 0.89 (m, 11H). LCMS (Method 15): 1.93 min, 689.2 $[M+H]^+$.

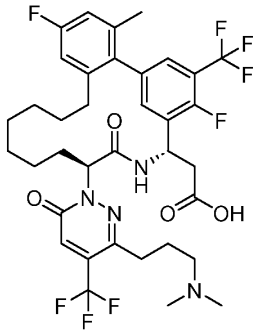
**Example 208:** 2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001547]** Prepared in an analogous manner to **Example 27** using **Intermediate 1128** (0.10 g, 0.14 mmol) and lithium hydroxide (10 mg, 0.42 mmol) in THF (1.3 mL), MeOH (1.3 mL) and water (0.9 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250

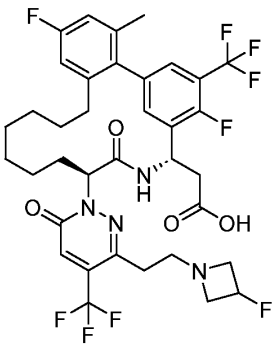
mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (43 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.60 (dd, 1H), 7.30 (dd, 1H), 7.24 (s, 1H), 6.96 – 6.85 (m, 2H), 5.81 (dd, 1H), 5.46 (dd, 1H), 2.98 – 2.25 (m, 15H), 2.20 (s, 3H), 2.08 – 1.99 (m, 2H), 1.99 (s, 3H), 1.68 – 1.55 (m, 1H), 1.54 – 0.93 (m, 10H). LCMS (Method 15): 1.96 min, 691.3 $[M+H]^+$.

**Example 209:** 2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



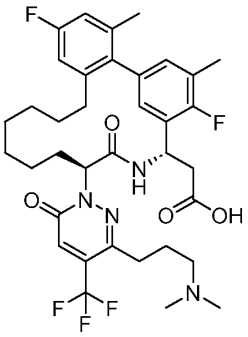
**[001548]** Prepared in an analogous manner to **Example 27** using **Intermediate 1136** (31 mg, 20 µmol) and lithium hydroxide (0.72 mg, 30 µmol) in THF (1.4 mL), MeOH (0.5 mL) and water (0.3 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (1.6 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.67 (dd, 1H), 7.31 (s, 1H), 7.28 (dd, 1H), 6.95 – 6.83 (m, 2H), 5.77 (dd, 1H), 5.39 (dd, 1H), 2.83 (t, 2H), 2.74 (dd, 1H), 2.62 (dd, 1H), 2.57 – 2.31 (m, 5H), 2.31 (s, 6H), 2.09 – 2.01 (m, 1H), 2.01 (s, 3H), 2.01 – 1.90 (m, 1H), 1.86 – 1.72 (m, 1H), 1.62 – 0.82 (m, 10H). LCMS (Method 15): 2.03 min, 745.3 $[M+H]^+$.

**Example 210:** 2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



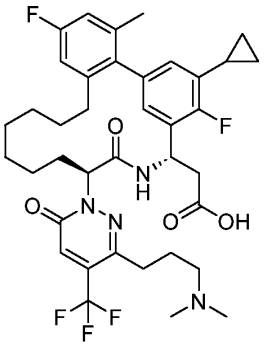
**[001549]** Prepared in an analogous manner to **Example 27** using **Intermediate 1142** (27 mg, 14 µmol) and lithium hydroxide (0.52 mg, 22 µmol) in THF (0.7 mL), MeOH (0.3 mL) and water (0.2 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (3.9 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.63 (dd, 1H), 7.35 (s, 1H), 7.32 (dd, 1H), 6.96 – 6.84 (m, 2H), 5.85 (dd, 1H), 5.47 (dd, 1H), 5.41 – 5.18 (m, 1H), 4.25 – 3.99 (m, 2H), 3.89 – 3.64 (m, 2H), 3.49 – 3.20 (m, 2H), 3.07 – 2.87 (m, 2H), 2.70 (dd, 1H), 2.59 (dd, 1H), 2.50 – 2.24 (m, 3H), 2.01 (s, 3H), 1.76 – 1.62 (m, 1H), 1.58 – 0.81 (m, 10H). LCMS (Method 15): 1.72 min, 761.3 $[M+H]^+$.

**Example 211:** 2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



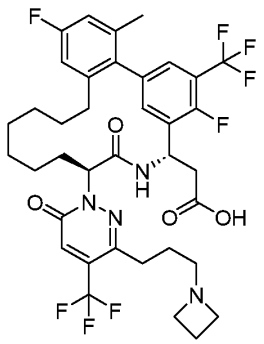
**[001550]** Prepared in an analogous manner to **Example 27** using **Intermediate 1146** (72 mg, 0.10 mmol) and lithium hydroxide (7.2 mg, 0.30 mmol) in THF (1.0 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (4.9 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.32 (s, 1H), 7.14 (d, 1H), 6.97 – 6.76 (m, 3H), 5.79 (t, 1H), 5.40 (dd, 1H), 2.84 (t, 2H), 2.76 – 2.59 (m, 3H), 2.53 (dd, 1H), 2.47 (s, 6H), 2.47 – 2.33 (m, 3H), 2.32 (s, 3H), 2.13 – 2.00 (m, 2H), 1.99 (s, 3H), 1.79 – 1.64 (m, 1H), 1.57 – 0.84 (m, 10H). LCMS (Method 15): 1.79 min, 691.3 $[M+H]^+$.

**Example 212:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(3-(3-(dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



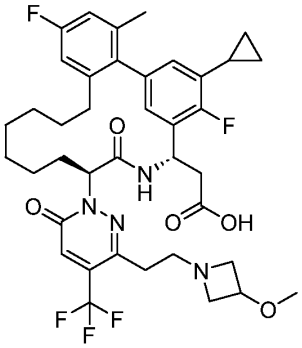
**[001551]** Prepared in an analogous manner to **Example 27** using **Intermediate 1150** (29 mg, 39 μmol) and lithium hydroxide (2.8 mg, 0.12 mmol) in THF (1.0 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (4.5 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.32 (s, 1H), 7.08 (dd, 1H), 6.90 – 6.78 (m, 2H), 6.53 (dd, 1H), 5.85 (dd, 1H), 5.42 (dd, 1H), 2.97 – 2.73 (m, 4H), 2.70 – 2.45 (m, 8H), 2.44 – 2.28 (m, 3H), 2.24 – 2.02 (m, 3H), 1.97 (s, 3H), 1.75 – 1.61 (m, 1H), 1.56 – 0.87 (m, 12H), 0.80 – 0.63 (m, 2H). LCMS (Method 15): 2.02 min, 717.3 $[M+H]^+$.

**Example 213:** 2-((3*S*,6*S*)-6-(3-(3-(Azetidin-1-yl)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



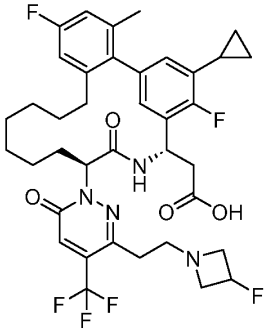
**[001552]** Prepared in an analogous manner to **Example 27** using **Intermediate 1154** (87 mg, 0.10 mmol) and lithium hydroxide (12 mg, 0.52 mmol) in THF (1.7 mL), MeOH (0.9 mL) and water (0.9 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 μm, eluting 50-60% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (42 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.64 (dd, 1H), 7.32 (s, 1H), 7.29 (dd, 1H), 6.96 – 6.84 (m, 2H), 5.81 (t, 1H), 5.40 (dd, 1H), 3.62 – 3.40 (m, 2H), 2.82 (t, 2H), 2.78 – 2.71 (m, 2H), 2.71 (dd, 1H), 2.59 (dd, 1H), 2.50 – 2.41 (m, 1H), 2.40 – 2.28 (m, 2H), 2.27 – 2.14 (m, 2H), 2.01 (s, 3H), 1.95 – 1.79 (m, 2H), 1.78 – 1.65 (m, 1H), 1.56 – 0.84 (m, 12H). LCMS (Method 15): 2.02 min, 757.3 $[M+H]^+$.

**Example 214:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001553]** Prepared in an analogous manner to **Example 27** using **Intermediate 1157** (27 mg, 35 µmol) and lithium hydroxide (2.5 mg, 0.11 mmol) in THF (0.5 mL), MeOH (0.5 mL) and water (0.2 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (5.9 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.37 (s, 1H), 7.06 (dd, 1H), 6.90 – 6.79 (m, 2H), 6.57 (dd, 1H), 5.89 (dd, 1H), 5.54 (dd, 1H), 4.54 – 4.20 (m, 2H), 4.06 – 3.07 (m, 2H), 3.65 – 3.42 (m, 1H), 3.41 (s, 3H), 3.38 – 3.29 (m, 2H), 3.16 – 2.95 (m, 2H), 2.61 (dd, 1H), 2.51 (dd, 1H), 2.44 – 2.26 (m, 3H), 2.24 – 2.12 (m, 1H), 1.97 (s, 3H), 1.75 – 0.88 (m, 13H), 0.82 – 0.63 (m, 2H). LCMS (Method 15): 1.72 min, 745.3 $[M+H]^+$.

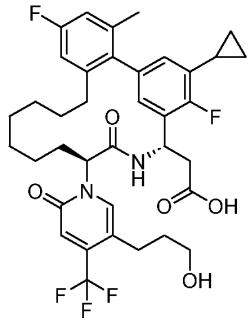
**Example 215:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001554]** Prepared in an analogous manner to **Example 27** using **Intermediate 1159** (25 mg, 33 µmol) and lithium hydroxide (2.4 mg, 0.10 mmol) in THF (0.5 mL), MeOH (0.5 mL) and water (0.2 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18 30 x 250 mm 5 µm, eluting 35-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (8.5 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.36 (s, 1H), 7.07 (dd, 1H), 6.90 – 6.79

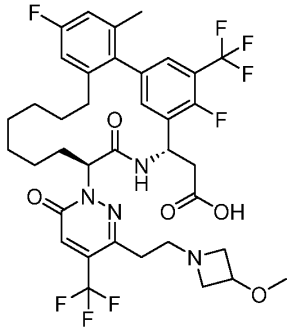
(m, 2H), 6.56 (dd, 1H), 5.89 (dd, 1H), 5.51 (dd, 1H), 5.50 – 5.52 (m, 1H), 4.47 – 4.27 (m, 2H), 4.13 – 3.90 (m, 2H), 3.62 – 3.38 (m, 2H), 3.14 – 2.86 (m, 2H), 2.64 (dd, 1H), 2.52 (dd, 1H), 2.44 – 2.26 (m, 3H), 2.25 – 2.12 (m, 1H), 1.97 (s, 3H), 1.72 – 0.95 (m, 13H), 0.88 – 0.64 (m, 2H). LCMS (Method 15): 1.73 min, 733.3 $[M+H]^+$.

**Example 216:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(3-hydroxypropyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001555]** Prepared in an analogous manner to **Example 27** using **Intermediate 757** (27 mg, 27 μmol) and lithium hydroxide (3.2 mg, 0.13 mmol) in THF (0.7 mL), MeOH (0.3 mL) and water (0.3 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 μm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (14 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.91 (s, 1H), 7.11 (d, 1H), 6.89 – 6.78 (m, 3H), 6.54 (d, 1H), 5.88 (dd, 1H), 5.52 (dd, 1H), 3.65 (t, 2H), 2.73 – 2.51 (m, 4H), 2.48 – 2.30 (m, 2H), 2.26 – 2.13 (m, 2H), 1.98 (s, 3H), 1.89 – 1.77 (m, 2H), 1.67 – 0.85 (m, 13H), 0.79 – 0.62 (m, 2H). LCMS (Method 15): 1.69 min, 689.2 $[M+H]^+$.

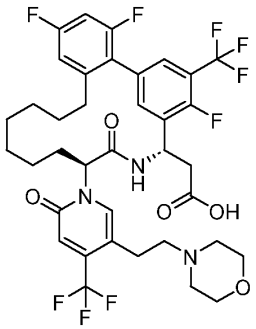
**Example 217:** 2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001556]** Prepared in an analogous manner to **Example 27** using **Intermediate 715** (38 mg, 43 μmol) and lithium hydroxide (1.6 mg, 65 μmol) in THF (1.0 mL), MeOH (0.3 mL) and

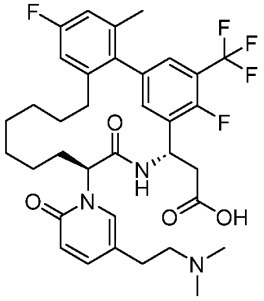
water (0.3 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (12 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.66 (dd, 1H), 7.33 (s, 1H), 7.30 (dd, 1H), 6.96 – 6.84 (m, 2H), 5.80 (t, 1H), 5.42 (dd, 1H), 4.24 – 4.06 (m, 1H), 4.01 – 3.65 (m, 2H), 3.31 (s, 3H), 3.31 – 3.17 (m, 2H), 3.16 – 3.00 (m, 2H), 2.98 – 2.81 (m, 2H), 2.73 (dd, 1H), 2.61 (dd, 1H), 2.51 – 2.26 (m, 3H), 2.01 (s, 3H), 1.84 – 1.67 (m, 1H), 1.56 – 0.95 (m, 10H). LCMS (Method 15): 1.77 min, 773.3 $[M+H]^+$.

**Example 218:** 2-((3*S*,6*S*)-1$^4$,1$^6$,2$^4$-Trifluoro-6-(5-(2-morpholinoethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



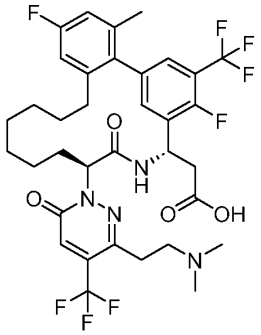
**[001557]** Prepared in an analogous manner to **Example 27** using **Intermediate 718** (47 mg, 52 µmol) and lithium hydroxide (3.7 mg, 0.16 mmol) in THF (1.0 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (25 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.04 (s, 1H), 7.71 (d, 1H), 7.47 (d, 1H), 7.01 (d, 1H), 6.92 (dt, 1H), 6.85 (s, 1H), 5.91 (t, 1H), 5.52 (dd, 1H), 3.79 (t, 4H), 2.87 – 2.46 (m, 12H), 2.27 – 2.10 (m, 1H), 1.71 – 0.86 (m, 11H). LCMS (Method 15): 1.77 min, 776.3 $[M+H]^+$.

**Example 219:** 2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



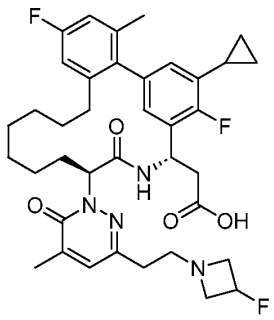
**[001558]** Prepared in an analogous manner to **Example 27** using **Intermediate 1160** (0.11 g, 0.16 mmol) and lithium hydroxide (11.5 mg, 0.48 mmol) in THF (1.0 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (20 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.65 (d, 1H), 7.57 (dd, 1H), 7.51 (dd, 1H), 7.33 (dd, 1H), 6.97 – 6.84 (m, 2H), 6.58 (d, 1H), 5.93 (dd, 1H), 5.55 (dd, 1H), 2.95 – 2.77 (m, 4H), 2.76 (s, 6H), 2.60 (dd, 1H), 2.50 – 2.37 (m, 2H), 2.35 – 2.13 (m, 2H), 1.99 (s, 3H), 1.68 – 0.89 (m, 11H). LCMS (Method 15): 1.72 min, 662.2 $[M+H]^+$.

**Example 220:** 2-((3*S*,6*S*)-6-(3-(2-(Dimethylamino)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



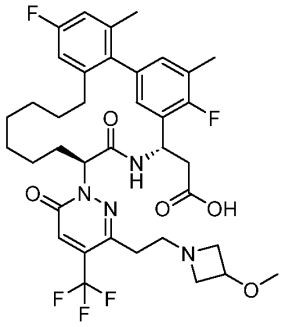
**[001559]** Prepared in an analogous manner to **Example 27** using **Intermediate 1161** (81 mg, 0.11 mmol) and lithium hydroxide (3.8 mg, 0.16 mmol) in THF (2.4 mL), MeOH (0.7 mL) and water (0.7 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (38 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.59 (dd, 1H), 7.39 (s, 1H), 7.34 (dd, 1H), 6.97 – 6.86 (m, 2H), 5.87 (dd, 1H), 5.52 (dd, 1H), 3.53 – 3.34 (m, 2H), 3.28 – 3.08 (m, 2H), 2.84 (s, 6H), 2.63 (dd, 1H), 2.54 (dd, 1H), 2.49 – 2.39 (m, 1H), 2.39 – 2.24 (m, 2H), 2.00 (s, 3H), 1.76 – 1.59 (m, 1H), 1.56 – 1.01 (m, 10H). LCMS (Method 15): 1.80 min, 731.2 $[M+H]^+$.

**Example 221:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



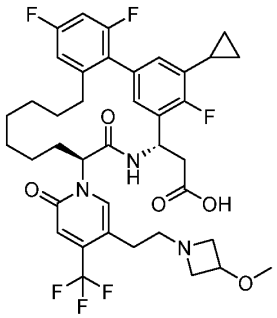
**[001560]** Prepared in an analogous manner to **Example 27** using **Intermediate 1162** (32 mg, 46 µmol) and lithium hydroxide (1.6 mg, 69 µmol) in THF (0.8 mL), MeOH (0.2 mL) and water (0.2 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (9 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.27 (d, 1H), 7.06 (dd, 1H), 6.90 – 6.78 (m, 2H), 6.56 (dd, 1H), 5.84 (dd, 1H), 5.56 (dd, 1H), 5.51 – 5.27 (m, 1H), 4.52 – 4.31 (m, 2H), 4.17 – 3.90 (m, 2H), 3.52 – 3.41 (m, 2H), 3.00 – 2.79 (m, 2H), 2.62 (dd, 1H), 2.51 – 2.21 (m, 4H), 2.20 (s, 3H), 2.20 – 2.11 (m, 1H), 1.97 (s, 3H), 1.62 – 1.49 (m, 2H), 1.47 – 0.84 (m, 11H), 0.80 – 0.63 (m, 2H). LCMS (Method 15): 1.62 min, 679.3 $[M+H]^+$.

**Example 222:** 2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



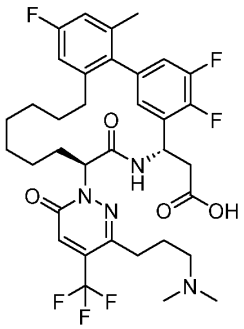
**[001561]** Prepared in an analogous manner to **Example 27** using **Intermediate 1165** (76 mg, 99 µmol) and lithium hydroxide (3.6 mg, 0.15 mmol) in THF (2.3 mL), MeOH (0.7 mL) and water (0.7 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (31 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.34 (s, 1H), 7.14 (dd, 1H), 6.91 – 6.78 (m, 3H), 5.80 (dd, 1H), 5.45 (dd, 1H), 4.29 – 4.12 (m, 1H), 4.11 – 3.87 (m, 2H), 3.51 – 3.38 (m, 2H), 3.34 (s, 3H), 3.27 – 3.14 (m, 2H), 3.02 – 2.86 (m, 2H), 2.65 (dd, 1H), 2.55 (dd, 1H), 2.47 – 2.33 (m, 3H), 2.33 (s, 3H), 2.00 (s, 3H), 1.81 – 1.64 (m, 1H), 1.60 – 0.92 (m, 10H). LCMS (Method 15): 1.76 min, 719.3 $[M+H]^+$.

**Example 223:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,1$^6$,2$^4$-trifluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001562]** Prepared in an analogous manner to **Example 27** using **Intermediate 1170** (0.11 g, 90 µmol) and lithium hydroxide (6.5 mg, 0.27 mmol) in THF (2.5 mL), MeOH (1.0 mL) and water (0.8 mL) at RT for 2 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (40 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.85 (s, 1H), 7.14 (dd, 1H), 6.95 (d, 1H), 6.89 (s, 1H), 6.84 (dt, 1H), 6.69 (dd, 1H), 5.98 (dd, 1H), 5.54 (dd, 1H), 4.36 – 4.14 (m, 3H), 3.89 – 3.63 (m, 2H), 3.37 (s, 3H), 3.32 – 3.17 (m, 2H), 2.97 – 2.84 (m, 1H), 2.81 – 2.69 (m, 1H), 2.64 (dd, 1H), 2.53 – 2.32 (m, 2H), 2.30 – 2.14 (m, 2H), 1.68 – 1.49 (m, 2H), 1.49 – 0.97 (m, 12H), 0.83 – 0.67 (m, 2H). LCMS (Method 15): 1.74 min, 748.3 $[M+H]^+$.

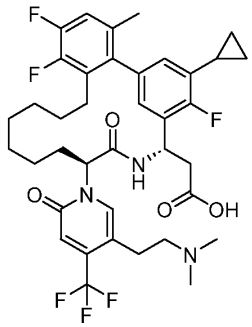
**Example 224:** 2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$,2$^5$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001563]** Prepared in an analogous manner to **Example 27** using **Intermediate 1174** (30 mg, 42 µmol) and lithium hydroxide (2.0 mg, 83 µmol) in THF (0.5 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (5 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.34 (s, 1H), 7.06 (d, 1H), 6.98 – 6.83 (m, 3H), 5.89 (dd, 1H), 5.44 (dd, 1H), 3.16 – 2.92 (m, 2H), 2.90 – 2.82 (m, 2H), 2.80 (s, 6H), 2.58

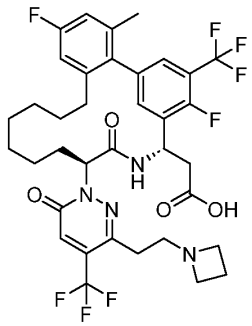
(dd, 1H), 2.48 (dd, 1H), 2.44 – 2.30 (m, 3H), 2.26 – 2.06 (m, 2H), 2.00 (s, 3H), 1.69 – 1.56 (m, 1H), 1.54 – 1.03 (m, 10H). LCMS (Method 15): 1.71 min, 695.3 $[M+H]^+$.

**Example 225:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^3$,1$^4$,2$^4$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001564]** Prepared in an analogous manner to **Example 27** using **Intermediate 1184** (95 mg, 52 µmol) and lithium hydroxide (10 mg, 0.42 mmol) in THF (1.0 mL), MeOH (1.0 mL) and water (1.0 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (4.5 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.94 (s, 1H), 7.11 (dd, 1H), 7.00 (dd, 1H), 6.87 (s, 1H), 6.55 (dd, 1H), 5.90 (dd, 1H), 5.51 (dd, 1H), 2.95 – 2.59 (m, 5H), 2.52 (dd, 1H), 2.49 (s, 6H), 2.31 – 2.13 (m, 3H), 1.94 (s, 3H), 1.69 – 0.89 (m, 14H), 0.80 – 0.63 (m, 2H). LCMS (Method 15): 1.83 min, 720.3 $[M+H]^+$.

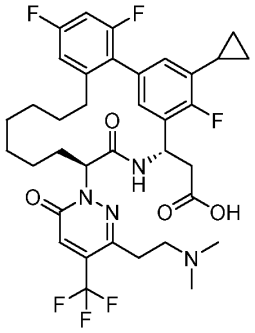
**Example 226:** 2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001565]** Prepared in an analogous manner to **Example 27** using **Intermediate 1185** (36 mg, 36 µmol) and lithium hydroxide (1.3 mg, 55 µmol) in THF (1.1 mL), MeOH (0.3 mL) and water (0.3 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 µm, eluting 40-50% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title

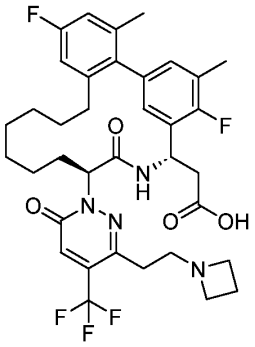
compound (5.2 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.61 (dd, 1H), 7.37 (s, 1H), 7.34 (dd, 1H), 6.97 – 6.85 (m, 2H), 5.91 (dd, 1H), 5.54 (dd, 1H), 4.31 – 3.74 (m, 4H), 3.63 – 3.32 (m, 2H), 3.31 – 2.90 (m, 2H), 2.65 (dd, 1H), 2.57 (dd, 1H), 2.52 – 2.23 (m, 5H), 2.01 (s, 3H), 1.76 – 1.58 (m, 1H), 1.57 – 1.01 (m, 10H). LCMS (Method 15): 2.02 min, 743.3 $[M+H]^+$.

**Example 227:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(3-(2-(dimethylamino)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,1$^6$,2$^4$-trifluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



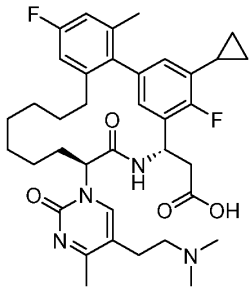
**[001566]** Prepared in an analogous manner to **Example 27** using **Intermediate 1191** (85 mg, 90 µmol) and lithium hydroxide (6.5 mg, 0.27 mmol) in THF (2.5 mL), MeOH (1.0 mL) and water (0.8 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 µm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (22 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.38 (s, 1H), 7.15 (d, 1H), 6.94 (d, 1H), 6.83 (dt, 1H), 6.67 (d, 1H), 5.87 (dd, 1H), 5.51 (dd, 1H), 3.49 – 3.34 (m, 2H), 3.28 – 3.06 (m, 2H), 2.83 (s, 6H), 2.66 – 2.41 (m, 4H), 2.37 – 2.24 (m, 1H), 2.23 – 2.13 (m, 1H), 1.76 – 1.60 (m, 1H), 1.60 – 0.96 (m, 12H), 0.80 – 0.66 (m, 2H). LCMS (Method 15): 1.89 min, 707.3 $[M+H]^+$.

**Example 228:** 2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



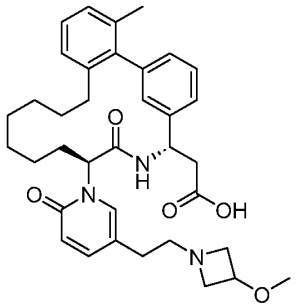
**[001567]** Prepared in an analogous manner to **Example 27** using **Intermediate 1192** (55 mg, 73 μmol) and lithium hydroxide (3.0 mg, 0.12 mmol) in THF (0.8 mL), MeOH (0.8 mL) and water (0.4 mL) at RT for 1.5 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 μm, eluting 35-45% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (20 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.38 (s, 1H), 7.08 (dd, 1H), 6.94 – 6.81 (m, 3H), 5.94 (dd, 1H), 5.59 (dd, 1H), 4.55 – 3.98 (m, 4H), 3.78 – 3.53 (m, 2H), 3.18 – 2.99 (m, 2H), 2.72 – 2.44 (m, 4H), 2.44 – 2.27 (m, 6H), 1.99 (s, 3H), 1.68 – 1.47 (m, 2H), 1.46 – 0.97 (m, 9H). LCMS (Method 15): 1.93 min, 689.2 $[M+H]^+$.

**Example 229:** 2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyrimidin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



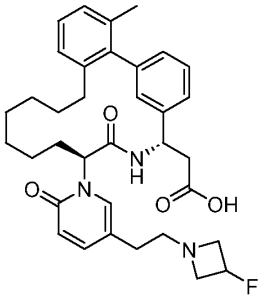

**[001568]** Prepared in an analogous manner to **Example 27** using **Intermediate 1195** (0.12 g, 0.17 mmol) and lithium hydroxide (13 mg, 0.52 mmol) in THF (4.8 mL), MeOH (2.2 mL) and water (0.8 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 μm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (28 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.01 (s, 1H), 7.03 (dd, 1H), 6.91 – 6.79 (m, 2H), 6.57 (dd, 1H), 5.95 (dd, 1H), 5.29 (dd, 1H), 3.44 – 3.10 (m, 2H), 3.03 – 2.80 (m, 2H), 2.80 (s, 6H), 2.63 (dd, 1H), 2.45 (s, 3H), 2.44 – 2.29 (m, 2H), 2.27 – 2.13 (m, 3H), 1.96 (s, 3H), 1.71 – 1.48 (m, 2H), 1.45 – 0.96 (m, 11H), 0.81 – 0.65 (m, 2H). LCMS (Method 15): 1.77 min, 649.3 $[M+H]^+$.

**Example 230:** 2-((3*S*,6*S*)-6-(5-(2-(3-Methoxyazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001569]** Prepared in an analogous manner to **Example 27** using **Intermediate 1198** (0.15 g, 0.24 mmol) and lithium hydroxide (17 mg, 0.72 mmol) in THF (1.0 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 µm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (63 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.69 (s, 1H), 7.50 – 7.35 (m, 3H), 7.31 (s, 1H), 7.22 – 6.95 (m, 4H), 6.55 (d, 1H), 5.65 – 5.34 (m, 2H), 4.22 – 4.10 (m, 1H), 4.07 – 3.82 (m, 2H), 3.49 – 3.34 (m, 2H), 3.32 (s, 3H), 3.10 – 2.92 (m, 2H), 2.90 – 2.47 (m, 4H), 2.46 – 2.28 (m, 2H), 2.27 – 2.13 (m, 1H), 1.99 (s, 3H), 1.62 – 0.92 (m, 11H). LCMS (Method 15): 1.57 min, 600.3 $[M+H]^+$.

**Example 231:** 2-((3*S*,6*S*)-6-(5-(2-(3-Fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid



**[001570]** Prepared in an analogous manner to **Example 27** using **Intermediate 1201** (0.15 g, 0.25 mmol) and lithium hydroxide (18 mg, 0.74 mmol) in THF (1.0 mL), MeOH (0.5 mL) and water (0.5 mL) at RT for 1 h. Purified by preparative HPLC (XBridge C18, 30 x 250 mm 5 µm, eluting 30-40% MeCN in 0.1% aqueous ammonia over 15 min) to provide the title compound (63 mg). $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.70 (s, 1H), 7.51 – 7.35 (m, 3H), 7.31 (s, 1H), 7.21 – 6.97 (m, 4H), 6.54 (d, 1H), 5.64 – 5.34 (m, 2H), 5.32 – 5.10 (m, 1H), 4.05 – 3.86 (m, 2H), 3.67 – 3.47 (m, 2H), 3.05 – 2.93 (m, 2H), 2.90 – 2.27 (m, 6H), 2.27 – 2.12 (m, 1H), 1.99 (s, 3H), 1.61 – 0.94 (m, 11H). LCMS (Method 15): 1.56 min, 588.3 $[M+H]^+$.

## Biological Testing

Cell Adhesion Assays

**[001571]** Cell adhesion assays were used to measure the ability of the compounds described herein to inhibit the interaction of α4β7 receptors and MAdCAM ligand, or α4β1 receptors and VCAM ligand. RPMI8866 cells express high levels of α4β7 and low levels of α4β1 receptors, and Jurkat cells express high levels of α4β1 and low levels of α4β7 (DOI: 10.1124/jpet.102.047704). The assays described are as follows:

**Assay 1**: adhesion of RPMI8866 cells to immobilized MAdCAM in the presence of high protein levels, using a luminescence endpoint

**Assay 2**: adhesion of RPMI8866 cells to immobilized MAdCAM in the presence of low protein levels, using a radiometric endpoint

**Assay 3**: adhesion of RPMI8866 cells to immobilized MAdCAM in the presence of high protein levels, using a radiometric endpoint

**Assay 4**: adhesion of Jurkat cells to immobilized VCAM in the presence of high protein levels, using a luminescence endpoint.

**[001572]** The assay results are provided in Tables 1 and 2 as mean $IC_{50}$ values ($n \geq 2$).

**Assay 1**

**[001573]** To coat the assay plates with ligand, 20 µL recombinant human MAdCAM-1 Fc chimera protein (Biotechne) at 3 µg/ml in PBS was added to wells of 384-well white cell culture assay plates (Corning 3570), which were sealed and incubated overnight at 22°C. The following day, solution was removed from the wells by flicking the plates, and the wells were then blocked by incubation with 30 µL PUCKS buffer (5.37 mM KCl, 137 mM NaCl, 4 mM $NaHCO_3$, 5.5 mM D-glucose, 25 mM HEPES (pH7.0)) containing 1% (w/v) BSA for 1 hour at room temperature. Meanwhile, ECHO acoustic dispensing was used to prepare compound plates containing dose-response curves of doubling dilutions of compounds at twice the desired final assay concentration in PUCKS buffer containing 4% (w/v) HSA and 0.6% (v/v) DMSO. After removal of blocking solution from the assay plates, 10 µL was transferred from the compound plates to the assay plates using a BIOMEK liquid handler. RPMI8866 cells were harvested by centrifugation and resuspended at 4 x 106 cells / mL in PBS + 2 mM MnCl2. 10 µL cell suspension was then added per well to the assay plates and incubated for 1 hour at 22°C. Final conditions in the adhesion step were 40 000 cells / well, 2% (w/v) HSA, 0.3% (v/v) DMSO and 1 mM MnCl2. After removal of the solutions and washing of the wells thrice with 20 µL PUCKS + 1% (w/v) BSA, 20 µL CellTiter-Glo reagent (Promega) was added to the wells and plates were incubated for 1 hour in the dark at room temperature. Luminescence was read on a CLARIOstar (BMG Labtech) and % inhibition was calculated for each well, using 30 µM of the commercially available α4β1/α4β7 antagonist firategrast for 100% inhibition

controls, and no compound for 0% inhibition controls. IC50 values were calculated using Dotmatics studies using 4-parameter non-linear regression curve fit.

**Assay 2**

**[001574]** To label cells with tritiated methionine, RPMI8866 cells were harvested by centrifugation and resuspended in methionine-free RPMI media (Gibco) at a density of 500 000 cells / mL. 20 x 106 cells were then added to a T175 tissue culture flask in a total volume of 40 mL. 15 µCi / mL [3H]-methionine (Perkin Elmer) was added to the cells and they were incubated at 37°C, 5% CO2 overnight. To coat the assay plates with ligand, 50 µL recombinant human MAdCAM-1 Fc chimera protein (Biotechne) at 15 µg/ml in PBS was added to wells of 96-well Flashplates (Perkin Elmer), which were sealed and incubated overnight at room temperature. The following day, coating solution was removed from the plates by flicking and wells were blocked by adding 200 µL PBS plus 1% (w/v) BSA and incubating at room temperature for 1 hr. Blocking solutions were removed and wells were washed with PBS. Meanwhile, compound plates were prepared by dispensing dose-response curves of compound using a D300 digital dispenser (Tecan) into V-bottomed 96 well plates (Greiner) at twice final assay concentration and 1% (v/v) DMSO in PUCKS buffer containing 0.2% BSA. 50 µL compound dilutions were then added to the coated wells in the assay plate. RPMI8866 cells were harvested by centrifugation and washed once by resuspension in PBS, before resuspension of the cell pellet in 7 mL PUCKS buffer + 3 mM MnCl2. 50 µL cell suspension was then added per well to the assay plate which was sealed with a TopSealA plate seal (Perkin Elmer), and centrifuged briefly before reading using a MicroBeta TriLux reader (Perkin Elmer). Final conditions in the adhesion step were 0.1% BSA (w/v), 0.5% (v/v) DMSO and 1.5 mM MnCl2 in PUCKS buffer. % inhibition was calculated for each well, using 1 µM of the commercially available α4β1/α4β7 antagonist firategrast for 100% inhibition controls, and no compound for 0% inhibition controls. IC50 values were calculated using XLfit using 4-parameter non-linear regression curve fit.

**Assay 3**

**[001575]** This was performed as Assay 2 with the following modifications - wells were blocked with PBS plus 1% (w/v) HAS; and compounds were dispensed in PUCKS buffer containing 4% HSA, giving final conditions in the adhesion step of 2% HSA (w/v), 0.5% (v/v) DMSO and 1.5 mM MnCl2 in PUCKS buffer.

**Assay 4**

**[001576]** This was performed as Assay 1 with the following modifications - assay plates were coated with 20 µL recombinant human VCAM-1 protein (Biotechne) at 1.5 µg/ml in PBS; and Jurkat cells were used.

Table 1

| | α4β7 $IC_{50}$ (nM) | | | α4β1 $IC_{50}$ (nM) |
|---|---|---|---|---|
| Example | Assay 1 | Assay 2 | Assay 3 | Assay 4 |
| 1 | 6550 | - | - | >20570 |
| 2 | 3294 | - | - | >20570 |
| 3 | 927 | - | - | >20570 |
| 4 | 796 | - | - | >29510 |
| 5 | 3646 | - | - | >29510 |
| 6 | 7349 | - | - | >29510 |
| 7 | 464 | - | - | >17180 |
| 8 | 4729 | - | - | >14340 |
| 9 | 950 | - | - | >29510 |
| 10 | 4975 | - | - | >29510 |
| 11 | 160 | - | - | >29510 |
| 12 | 8295 | - | - | >29510 |
| 13 | 93 | - | - | >29510 |
| 14 | 2555 | - | - | >29510 |
| 15 | 299 | - | - | >29510 |
| 16 | 1196 | - | - | >29510 |
| 17 | 58 | - | - | >29510 |
| 18 | 51 | - | - | 17610 |
| 19 | 2105 | - | - | >29510 |
| 20 | 2117 | - | - | >29510 |
| 21 | 156 | - | - | >29510 |
| 22 | 2.7 | - | - | 3241 |
| 23 | 34 | - | - | 12000 |
| 24 | 1837 | - | - | >29510 |
| 25 | - | 3117 | | >29510 |
| 26 | - | - | 1732 | >29510 |
| 27 | - | - | 1457 | >29510 |
| 28 | - | - | 1731 | >20570 |
| 29 | 161 | - | - | 29010 |
| 30 | 1.5 | - | - | 453 |
| 31 | 1.2 | - | - | 1492 |
| 32 | | - | 3584 | - |
| 33 | - | - | 1842 | >29510 |

Table 2

| Example | α4β7 $IC_{50}$ (nM) Assay 1 | α4β1 $IC_{50}$ (nM) Assay 4 | Example | α4β7 $IC_{50}$ (nM) Assay 1 | α4β1 $IC_{50}$ (nM) Assay 4 |
|---|---|---|---|---|---|
| 34 | 9.4 | 16900 | 133 | 32 | 28180 |
| 35 | 1.3 | 641 | 134 | 16 | 6761 |
| 36 | 6.4 | 11220 | 135 | 15 | 23990 |
| 37 | 0.7 | 683 | 136 | 13 | 14790 |
| 38 | 1.0 | 143 | 137 | 24 | 24830 |

| Example | α4β7 $IC_{50}$ (nM) Assay 1 | α4β1 $IC_{50}$ (nM) Assay 4 | Example | α4β7 $IC_{50}$ (nM) Assay 1 | α4β1 $IC_{50}$ (nM) Assay 4 |
|---|---|---|---|---|---|
| **39** | 8.7 | 3679 | **138** | 4.0 | 4121 |
| **40** | 4.5 | 4881 | **139** | 9.3 | >29510 |
| **41** | 2.3 | 2925 | **140** | 767 | >29510 |
| **42** | 14 | 24550 | **141** | 2.5 | 11220 |
| **43** | 2.2 | 1995 | **142** | 5.5 | 19140 |
| **44** | 11 | 1809 | **143** | 6.6 | 7244 |
| **45** | 20 | 10210 | **144** | 7.6 | 7413 |
| **46** | 4.9 | 1088 | **145** | 62 | >29510 |
| **47** | 4.1 | 4405 | **146** | 7.9 | 8066 |
| **48** | 16 | 5038 | **147** | 16 | 8577 |
| **49** | 2.9 | 871 | **148** | 3.9 | 2818 |
| **50** | 149 | >29510 | **149** | 20 | >29510 |
| **51** | 4.8 | 2671 | **150** | 12 | 24660 |
| **52** | 3.2 | 989 | **151** | 8.0 | 11660 |
| **53** | 1.3 | 206 | **152** | 851 | >29510 |
| **54** | 8.2 | 2380 | **153** | 5.9 | 20420 |
| **55** | 13 | 10960 | **154** | 19 | 20570 |
| **56** | 9.7 | 2651 | **155** | 9.8 | 19050 |
| **57** | 125 | >29510 | **156** | 16 | >29510 |
| **58** | 9.7 | 5821 | **157** | 16 | 1055 |
| **59** | 3.6 | 4842 | **158** | 232 | >29510 |
| **60** | 8.7 | 4501 | **159** | 6.5 | 24830 |
| **61** | 8.7 | >29510 | **160** | 44 | >29510 |
| **62** | 116 | 28510 | **161** | 3.0 | 9190 |
| **63** | 176 | >29510 | **162** | 184 | >29510 |
| **64** | 240 | >29510 | **163** | 6.0 | 20420 |
| **65** | 20 | >29510 | **164** | 5.3 | 687 |
| **66** | 290 | >29510 | **165** | 3.3 | 1259 |
| **67** | 5.7 | 6531 | **166** | 110 | 29170 |
| **68** | 5.8 | 5710 | **167** | 38 | 10470 |
| **69** | 4.6 | 2917 | **168** | 20 | 15490 |
| **70** | 29 | >29510 | **169** | 7.8 | 9404 |
| **71** | 285 | >29510 | **170** | 4.4 | 4193 |
| **72** | 3.8 | 4137 | **171** | 44 | 13300 |
| **73** | 74 | 28180 | **172** | 3.9 | 4169 |
| **74** | 25 | 20300 | **173** | 29 | >29510 |
| **75** | 107 | >29510 | **174** | 324 | >29510 |
| **76** | 38 | 20300 | **175** | 5.2 | 8128 |
| **77** | 185 | >29510 | **176** | 2754 | >29510 |
| **78** | 18 | 19350 | **177** | 531 | 18620 |
| **79** | 8.7 | 5248 | **178** | 16 | 10470 |
| **80** | 372 | 28400 | **179** | 7.3 | 6310 |
| **81** | 2163 | >29510 | **180** | 8.1 | >29510 |
| **82** | 3981 | >29510 | **181** | 902 | >29510 |
| **83** | 7.5 | 8318 | **182** | 5.5 | 905 |

| Example | α4β7 $IC_{50}$ (nM) Assay 1 | α4β1 $IC_{50}$ (nM) Assay 4 | Example | α4β7 $IC_{50}$ (nM) Assay 1 | α4β1 $IC_{50}$ (nM) Assay 4 |
|---|---|---|---|---|---|
| **84** | 21 | >29510 | **183** | 537 | >29510 |
| **85** | 8.5 | 2113 | **184** | 34 | >29510 |
| **86** | 59 | 24270 | **185** | 38 | >29510 |
| **87** | 22 | >29510 | **186** | 17 | 5329 |
| **88** | 62 | 24740 | **187** | 17 | 5591 |
| **89** | 174 | >29510 | **188** | 2018 | >29510 |
| **90** | 133 | >29510 | **189** | 3.4 | 12080 |
| **91** | 556 | >29510 | **190** | 2.4 | 8913 |
| **92** | 58 | >29510 | **191** | 3.4 | 12160 |
| **93** | 1479 | >29510 | **192** | 48 | 14960 |
| **94** | 17 | 7025 | **193** | 5012 | >29510 |
| **95** | 67 | 18620 | **194** | 7.8 | 27700 |
| **96** | 21 | 24550 | **195** | 188 | 29290 |
| **97** | 146 | >29510 | **196** | 490 | >29510 |
| **98** | 8.4 | 13180 | **197** | 4.3 | 3758 |
| **99** | 153 | >29510 | **198** | 34 | >29510 |
| **100** | 4.7 | 6839 | **199** | 26 | 11890 |
| **101** | 21 | >29510 | **200** | 1318 | >29510 |
| **102** | 5.1 | 4121 | **201** | 2239 | >29510 |
| **103** | 42 | >29510 | **202** | 3631 | >29510 |
| **104** | 6.6 | 6780 | **203** | 4.1 | 25120 |
| **105** | 52 | 28840 | **204** | 1549 | >29510 |
| **106** | 1514 | >29510 | **205** | 111 | >29510 |
| **107** | 7.1 | 10500 | **206** | 85 | >29510 |
| **108** | 9.7 | 3673 | **207** | 33 | >29510 |
| **109** | 3.8 | 700 | **208** | 19 | 25120 |
| **110** | 26 | >29510 | **209** | 5.8 | 25610 |
| **111** | 157 | >29510 | **210** | 111 | >29510 |
| **112** | 59 | 18200 | **211** | 1.9 | 10780 |
| **113** | 1862 | >29510 | **212** | 4.5 | 26100 |
| **114** | 32 | 25120 | **213** | 11 | 27540 |
| **115** | 7.2 | 22910 | **214** | 9.1 | 27860 |
| **116** | 68 | >29510 | **215** | 13 | 27120 |
| **117** | 43 | >29510 | **216** | 129 | >29510 |
| **118** | 12 | 16140 | **217** | 32 | >29510 |
| **119** | 16 | 16370 | **218** | 227 | >29510 |
| **120** | 20 | 11290 | **219** | 2.1 | 556 |
| **121** | 76 | >29510 | **220** | 7.3 | >29510 |
| **122** | 9.4 | 22390 | **221** | 57 | >29510 |
| **123** | 8.4 | 4315 | **222** | 13 | 28400 |
| **124** | 28 | 7244 | **223** | 55 | >29510 |
| **125** | 519 | >29510 | **224** | 7.6 | 25700 |
| **126** | 41 | >29510 | **225** | 18 | >29510 |
| **127** | 3.7 | 651 | **226** | 12 | >29510 |
| **128** | 178 | 27860 | **227** | 20 | >29510 |

| Example | α4β7 $IC_{50}$ (nM) Assay 1 | α4β1 $IC_{50}$ (nM) Assay 4 | Example | α4β7 $IC_{50}$ (nM) Assay 1 | α4β1 $IC_{50}$ (nM) Assay 4 |
|---|---|---|---|---|---|
| **129** | 269 | >29510 | **228** | 5.2 | >29510 |
| **130** | 4.2 | 562 | **229** | 2.5 | 2455 |
| **131** | 5.8 | 3467 | **230** | 7.9 | 23990 |
| **132** | 291 | >29510 | **231** | 42 | >29510 |

**[001577]** As can be seen from the data in Tables 1 and 2, the compounds of the present invention are potent α4β7 integrin inhibitors, and additionally show selectivity for α4β7 over α4β1.

Whole Blood Assays

**[001578]** Compounds were assessed for their ability to inhibit the interaction of MAdCAM or LDV with α4β7 or α4β1 respectively, on CD4+ cells using a human whole blood assay.

Human whole blood MadCAM assay (**Assay 5**)

**[001579]** Three-fold dose response curves of compounds were prepared in DMSO and diluted in PBS, so the compounds were at 10-fold the final assay concentration in PBS with 5% DMSO. 2.5 µl of these compound dilutions were mixed with 2.5 µl of human MAdCAM labelled with Alexa Fluor 647, diluted to 10x final assay concentration in PBS, in 96-well V bottom assay plates. Meanwhile, mouse anti-CD4 antibody labelled with Alexa Fluor 488 was added to fresh heparinised human blood along with Manganese (II) chloride solution. Then 20 µl of this whole blood mixture was added to the 5 µl compound/hMAdCAM mixture. The final assay concentrations were 4 mM Manganese and 1 µg/ml hMAdCAM. Following 1 hour of incubation, at room temperature in the dark, cells were pelleted by centrifugation. The cells were then resuspended in 200 µl of 1x lyse/fix solution, and incubated for 10 min at 37 °C, to lyse the red blood cells and fix the leukocytes. Following further centrifugation, the cell pellets were resuspended in 200 µl 0.5% formaldehyde in PBS, stored in the dark until analysis using a BD Accuri C6 flow cytometer. % inhibition was calculated for each well, using 10 µM of a potent α4β7 inhibitor for 100% inhibition controls, and no compound for 0% inhibition controls. IC50 values were calculated using 4-parameter non-linear regression curve fit.

Human whole blood LDV assay (**Assay 6**)

**[001580]** Three-fold dose response curves of compounds were prepared in DMSO and diluted in PBS, so the compounds were at 10-fold the final assay concentration in PBS with 5% DMSO. 5 µl of these compound dilutions were mixed with 5 µl of LDV-FITC diluted to 10x final assay concentration in PBS, in 96-well deep (0.5ml) V bottom plates. Meanwhile, mouse anti-CD4 antibody labelled with PE-Cy7 was added to fresh heparinised human blood along with Manganese (II) chloride solution. Then 40 µl of this whole blood mixture was added to the

10 µl compound/LDV mixture. The final assay concentrations were 4 mM Manganese and 1 µM LDV-FITC. Following 1 hour of incubation, at room temperature in the dark, cells were pelleted by centrifugation. The cells were then resuspended in 500 µl of 1x lyse/fix solution and incubated for 10 mins at 37 °C, to lyse the red blood cells and fix the leukocytes. Following further centrifugation, the cell pellets were washed twice with 250 µl of stain buffer. Finally, the cells were suspended in 200 µl 0.5% formaldehyde in PBS, stored in the dark until analysis using a BD Accuri C6 flow cytometer. % inhibition was calculated for each well, using 50 µM of BIO5192 for 100% inhibition controls, and no compound for 0% inhibition controls. $IC_{50}$ values were calculated using 4-parameter non-linear regression curve fit. The assay results are provided in Table 3 as mean $IC_{50}$ values (n≥2).

Table 3

| Example | α4β7 $IC_{50}$ (nM) Assay 5 | α4β1 $IC_{50}$ (nM) Assay 6 |
|---|---|---|
| **161** | 74 | >50000 |
| **180** | 74 | >50000 |

*In Vivo* PD Model

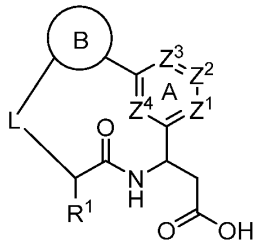
**[001581]** Compounds were assessed for their ability to inhibit the migration of T-cells into gastrointestinal tissue.

Mouse Gut Homing T-cell model

**[001582]** $\alpha4\beta7^{HI}$ cells were labelled with CellTrace™ Far Red. Cells were re-suspended in the stain diluted 1:1000 with PBS. Cells were incubated for 20 minutes at 37 °C and then washed with complete media. Then 50 million cells were injected into B6.SJL recipient mice, 15 minutes after PO dosing of compound or vehicle. In addition, DATK32, a mouse anti-α4β7 antibody was tested as a positive control in this model, along with an isotype control. With DATK32 and in its isotype control, mice were dosed one hour prior to the cell transfer. Two hours after cell transfer animals were euthanised and blood, spleen, mesenteric lymph and nodes were collected. Cells were stained with an antibody to detect $\alpha4\beta7^{HI}$ cells, then samples analysed by flow cytometry for $\alpha4\beta7^{HI}$ cells and CTRF dye. The percentage of total live cells that were $\alpha4\beta7^{HI}$ cells was calculated.

## Claims

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:




(I)

wherein:

A is an aromatic ring and $Z^1$, $Z^2$, $Z^3$ and $Z^4$ are independently N or $CR^2$;

B is aryl, 5- to 10-membered heteroaryl, $C_{3-10}$cycloalkyl, or 4- to 10-membered heterocyclyl; wherein B is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, cyano, hydroxyl, $NR^3R^4$, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-10}$cycloalkyl, and 4- to 10-membered heterocyclyl;

L is $C_{3-8}$alkylene, $C_{3-8}$alkenylene, or $C_{3-8}$alkynylene, wherein one, two or three methylene groups in L are optionally substituted with -O-, -S-, -C(O)-, or -N($R^5$)-; and wherein L is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, hydroxyl, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, and $NR^6R^7$;

$R^1$ is 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, aryl, $C_{3-10}$cycloalkyl, or $NR^8C(O)R^9$; wherein:

i) each of 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, aryl, and $C_{3-10}$cycloalkyl is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, oxo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{1-4}$alkylene-OH, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$; and

ii) the 4- to 10-membered heterocyclyl group optionally contains one or two carbon-carbon double bonds, and is optionally fused to a 5- or 6-membered heteroaryl ring, or a phenyl ring;

$R^2$ at each occurrence is independently selected from H, halo, cyano, hydroxyl, $C_{1-5}$alkyl, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-6}$cycloalkyl and 4-6 membered heterocyclyl;

$R^3$ and $R^4$ are independently selected from H, $C_{1-5}$alkyl, $C_{1-5}$haloalkyl, and $C_{3-10}$cycloalkyl;

$R^5$, $R^6$ and $R^7$ are independently H or $C_{1-5}$alkyl;

$R^8$ is H, $C_{1-6}$alkyl, $C_{2-6}$haloalkyl, $C_{2-4}$alkylene-O-$C_{1-4}$alkyl; $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, or $C_{2-5}$alkylene-$NR^{12}R^{13}$;

$R^9$ is $C_{1-6}$alkyl, $C_{1-6}$alkoxy, $C_{1-6}$haloalkyl, $C_{1-6}$haloalkoxy, $C_{2-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, $NR^{14}R^{15}$ or $C_{1-5}$alkylene-$NR^{16}R^{17}$;

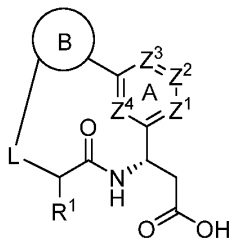
$R^{10}$ and $R^{11}$ are independently H, $C_{1-5}$alkyl, $C_{1-5}$haloalkyl or -$C_{1-4}$alkylene-O-$C_{1-4}$alkyl; or

$R^{10}$ and $R^{11}$, taken together with the nitrogen to which they are attached, form a 4- to 6-membered heterocyclyl ring optionally substituted with one to four groups independently selected from halo, $C_{1-5}$alkyl, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, and $C_{1-5}$haloalkoxy; and

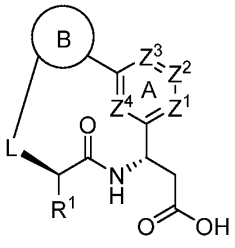
$R^{12}$, $R^{13}$, $R^{14}$, $R^{15}$, $R^{16}$, and $R^{17}$ are independently H, $C_{1-5}$alkyl, or $C_{1-5}$haloalkyl; or

$R^{12}$ and $R^{13}$, $R^{14}$ and $R^{15}$, or $R^{16}$ and $R^{17}$, taken together with the nitrogen atoms to which they are attached, independently form a 4- to 6-membered heterocyclyl ring optionally substituted with one to four groups independently selected from halo and $C_{1-5}$alkyl.

2. The compound according to claim 1, wherein the compound has a structure according to either formula IA or formula IB:




(IA)




(IB)

,

or a pharmaceutically acceptable salt thereof.

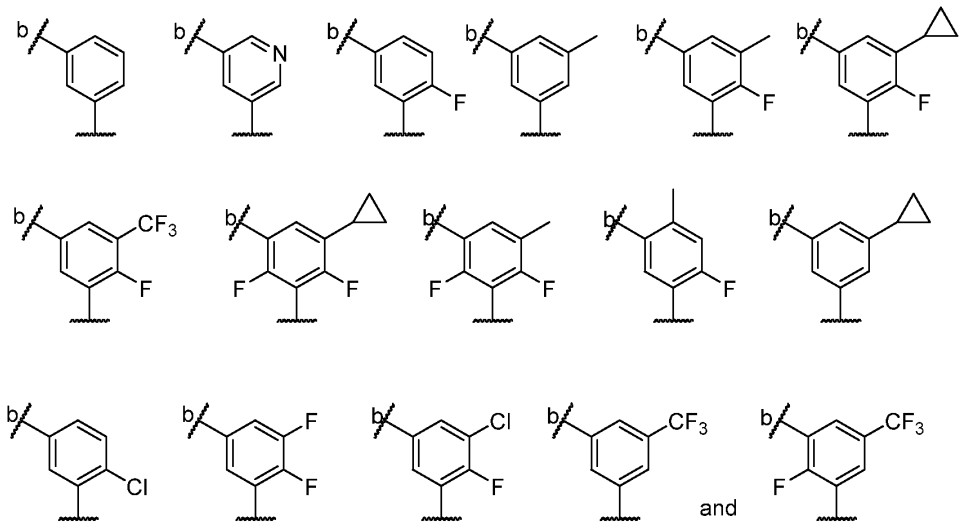
3. The compound according to claim 1 or claim 2, wherein $Z^1$, $Z^2$, $Z^3$ and $Z^4$ are all $CR^2$.

4. The compound according to claim 1 or claim 2, wherein one of $Z^1$, $Z^2$, $Z^3$ and $Z^4$ is N and the other three are $CR^2$.

5. The compound according to any one of claims 1 to 4, wherein $R^2$ at each occurrence is independently selected from H, halo, cyano, hydroxyl, $C_{1-5}$alkyl, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, and $C_{3-6}$cycloalkyl.

6. The compound according to claim 5, wherein $R^2$ at each occurrence is independently selected from H, fluoro, chloro, methyl, ethyl, trifluoromethyl, and cyclopropyl.

7. The compound according to claim 1 or claim 2, wherein A is selected from:



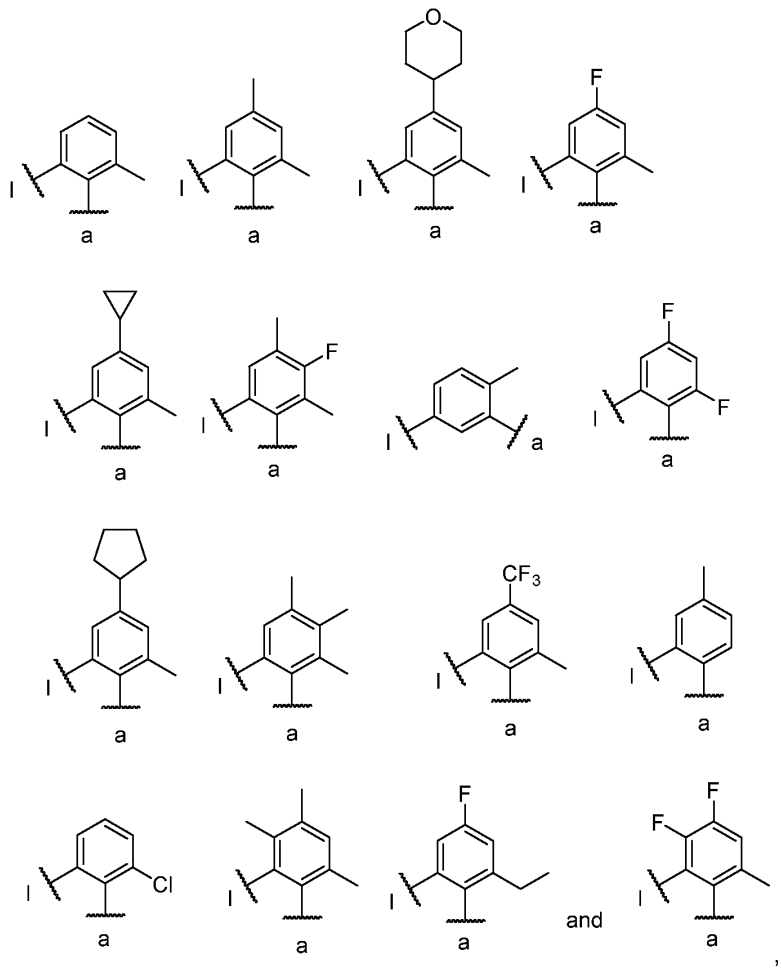

wherein 'b' is the point of attachment to the B ring.

8. The compound according to any one of claims 1 to 7, wherein B is aryl, or 5- to 6-membered heteroaryl; wherein B is optionally substituted with one to four substituents independently selected from $C_{1-3}$alkyl, halo, cyano, hydroxyl, $NR^3R^4$, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-7}$cycloalkyl, and 4- to 10-membered heterocyclyl.

9. The compound according to any one of claims 1 to 7, wherein B is phenyl, optionally substituted with one to four substituents independently selected from $C_{1-3}$alkyl, halo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{3-7}$cycloalkyl, and 4- to 10-membered heterocyclyl.

10. The compound according to any one of claims 1 to 7, wherein B is phenyl, optionally substituted with one to three substituents independently selected from methyl, fluoro, cyclopropyl, and 5- to 6-membered heterocyclyl.

11. The compound according to any one of claims 1 to 7, wherein B is selected from:



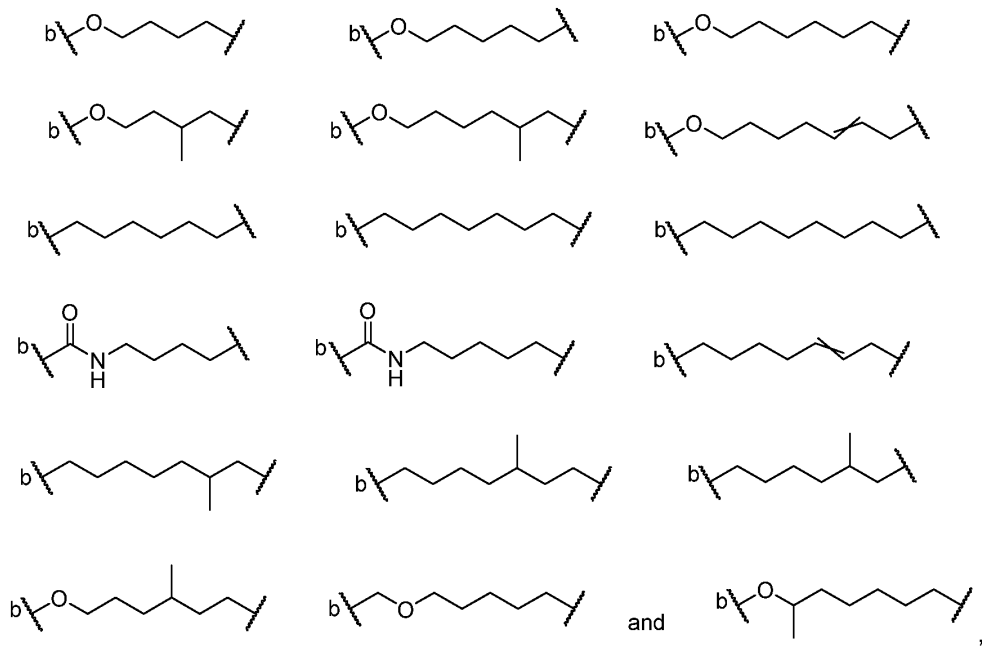

wherein 'a' is the point of attachment to the A ring and 'l' is the point of attachment to the linker L.

12. The compound according to any one of claims 1 to 11, wherein L is $C_{3-8}$alkylene, or $C_{3-8}$alkenylene, wherein one, two or three methylene groups in L are optionally substituted with -O-, -S-, -C(O)-, or -N($R^5$)-; and wherein L is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, hydroxyl, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, and $NR^6R^7$.

13. The compound according to any one of claims 1 to 11, wherein L is $C_{5-8}$alkylene, or $C_{5-8}$alkenylene, wherein one, two or three methylene groups in L are optionally substituted with -O-, -C(O)-, or -N($R^5$)-; and wherein L is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, hydroxyl, $C_{1-5}$alkoxy, and $C_{1-5}$haloalkyl.

14. The compound according to any one of claims 1 to 11, wherein L is $C_{5-8}$alkylene, wherein one or two methylene groups in L are optionally substituted with -O-, -C(O)-, or -N($R^5$)-; and wherein L is optionally substituted with one to three independently selected $C_{1-5}$alkyl substituents.

15. The compound according to any one of claims 1 to 11, wherein L is selected from:



wherein 'b' is the point of attachment to the B ring.

16. The compound according to any one of claims 1 to 15, wherein $R^1$ is 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, aryl, $C_{3-10}$cycloalkyl, or $NR^8C(O)R^9$; wherein:

i) each of 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, aryl, and $C_{3-10}$cycloalkyl is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, oxo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$; and

ii) the 4- to 10-membered heterocyclyl group optionally contains one or two carbon-carbon double bonds, and is optionally fused to a 5- or 6-membered heteroaryl ring, or a phenyl ring.

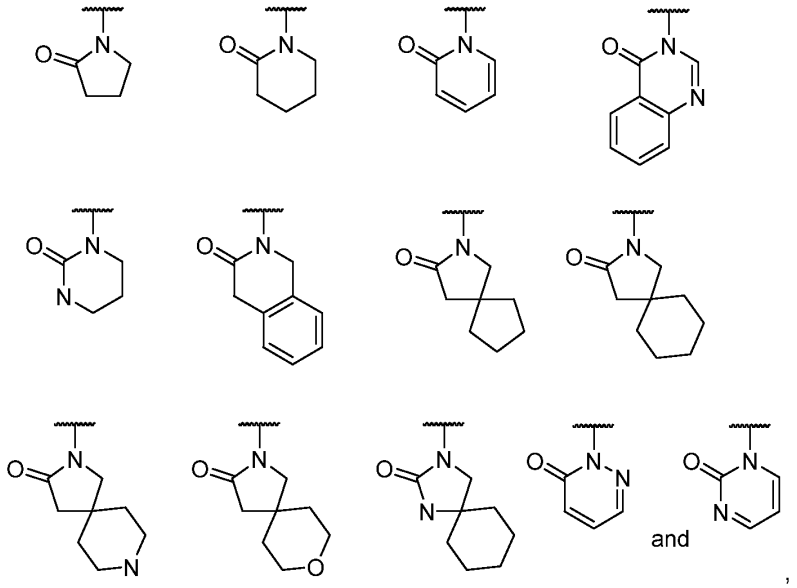
17. The compound according to any one of claims 1 to 15, wherein $R^1$ is 4- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or -$NR^8C(O)R^9$; wherein:

i) each of 4- to 10-membered heterocyclyl, and 5- to 10-membered heteroaryl is optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, oxo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$; and

ii) the 4- to 10-membered heterocyclyl group optionally contains one or two carbon-carbon double bonds, and is optionally fused to a 5- or 6-membered heteroaryl ring, or a phenyl ring.

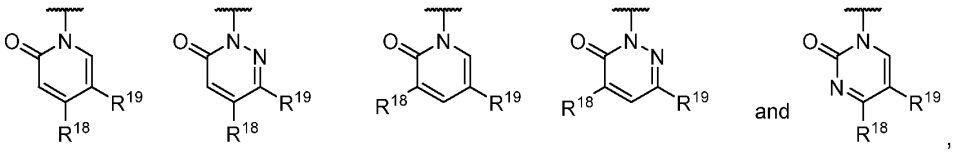
18. The compound according to any one of claims 1 to 15, wherein $R^1$ is 5- to 6-membered heterocyclyl; optionally substituted with one to five substituents independently selected from $C_{1-5}$alkyl, halo, oxo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$; optionally containing one or two carbon-carbon double bonds; and optionally fused to a phenyl ring.

19. The compound according to any one of claims 1 to 15, wherein $R^1$ is selected from:




optionally substituted with one to three substituents independently selected from $C_{1-5}$alkyl, halo, oxo, cyano, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, $C_{1-5}$haloalkoxy, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{1-4}$alkylene-OH, $C_{3-6}$cycloalkyl, 4- to 6-membered heterocyclyl, and $C_{1-4}$alkylene-$NR^{10}R^{11}$.

20. The compound according to any one of claims 1 to 15, wherein $R^1$ is selected from:



wherein $R^{18}$ is selected from hydrogen, $C_{1-5}$alkyl, halo, $C_{1-5}$alkoxy, $C_{1-5}$haloalkyl, and $C_{3-6}$cycloalkyl; and $R^{19}$ is selected from hydrogen, halo, $C_{1-4}$alkylene-O-$C_{1-4}$alkyl, $C_{1-4}$alkylene-OH, and $C_{1-4}$alkylene-$NR^{10}R^{11}$.

21. The compound according to any one of claims 1 to 15, wherein $R^1$ is $NR^8C(O)R^9$, and $R^8$ is H or $C_{1-6}$alkyl.

22. The compound according to any one of claims 1 to 15 or claim 21, wherein $R^1$ is $NR^8C(O)R^9$, and $R^9$ is $C_{1-6}$alkyl.

23. The compound according to any one of claims 1 to 22, wherein $R^{10}$ and $R^{11}$ are independently H or $C_{1-5}$alkyl.

24. The compound according to any one of claims 1 to 22, wherein $R^{10}$ and $R^{11}$, taken together with the nitrogen to which they are attached, form a 4- to 6-membered heterocyclyl ring optionally substituted with one to four groups independently selected from halo, $C_{1-5}$alkyl, $C_{1-5}$alkoxy, and $C_{1-5}$haloalkyl.

25. A compound selected from one of the following compounds, or a pharmaceutically acceptable salt thereof:

2-((9*S*,12*S*)-9-Acetamido-$2^6$-methyl-10-oxo-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid;

2-((8*S*,11*S*)-8-Acetamido-$2^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid;

2-((10*S*,13*S*)-10-Acetamido-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-Acetamido-$2^6$,8-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-acetamido-$2^6$-methyl-11-oxo-3-oxa-12-aza-1,2(1,3)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((8*S*,11*S*)-8-Acetamido-$2^6$,6-dimethyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid;

2-((10*S*,13*S*)-$2^6$-Methyl-10-(*N*-methylacetamido)-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6*S*)-$1^6$-Methyl-6-(*N*-methylacetamido)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxopiperidin-1-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((9*S*,12*S*)-2$^6$-Methyl-10-oxo-9-(2-oxopiperidin-1-yl)-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid;

2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxopyrrolidin-1-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((8*S*,11*S*)-2$^6$-Methyl-9-oxo-8-(2-oxopyridin-1(2*H*)-yl)-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid;

2-((10*S*,13*S*)-2$^4$-fluoro-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-Fluoro-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxopiperidin-1-yl)-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-2$^4$-Fluoro-2$^6$-methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(4-Fluoro-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxo-5-(trifluoromethyl)pyridin-1(2H)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-1$^4$-Fluoro-1$^5$,2$^6$-dimethyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((8*S*,11*S*)-8-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid;

2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxopyridin-1(2*H*)-yl)-2$^4$-(tetrahydro-2*H*-pyran-4-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6*S*)-6-Acetamido-1$^6$-methyl-5,12-dioxo-4,11-diaza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-Acetamido-1$^6$-methyl-5,13-dioxo-4,12-diaza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((11*S*,14*S*,*E*)-11-acetamido-2$^6$-methyl-12-oxo-3-oxa-13-aza-1(1,3),2(1,2)-dibenzenacyclotetradecaphan-8-en-14-yl)acetic acid;

2-((11*S*,14*S*)-11-Acetamido-2$^6$-methyl-12-oxo-3-oxa-13-aza-1(1,3),2(1,2)-dibenzenacyclotetradecaphane-14-yl)acetic acid;

2-((10*S*,13*S*)-2$^4$-Fluoro-2$^6$-methyl-10-(*N*-methylacetamido)-11-oxo-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-2$^4$-Fluoro-2$^6$-methyl-10-(*N*-methylacetamido)-11-oxo-3-oxa-12-aza-1(3,5)-pyridina-2(1,2)-benzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-2$^6$-Methyl-11-oxo-10-(4-oxoquinazolin-3(4*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^4$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(3-Fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-((*R*)-3-Fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(3-Methoxyazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Azetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-1$^4$,2$^4$-Difluoro-10-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-1$^4$-Fluoro-10-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^5$,2$^4$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-1$^4$,2$^4$-Difluoro-10-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^5$,2$^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-$1^4$-fluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-$1^4$,$2^4$-Difluoro-10-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid

2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^2$,$1^4$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-$1^4$-fluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-24-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-$1^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((8*S*,11*S*)-8-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-$2^4$-fluoro-$2^6$-methyl-9-oxo-3-oxa-10-aza-1(1,3),2(1,2)-dibenzenacycloundecaphane-11-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$-cyclopropyl-$1^2$,$1^4$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-$1^4$-fluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-10-(2-oxo-5-(3-(pyrrolidin-1-yl)propyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^5$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^2$,$1^4$-difluoro-$1^5$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-$1^5$-cyclopropyl-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^2$,$1^4$-difluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotetradecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-$1^5$-Cyclopropyl-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-$1^5$-Cyclopropyl-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-$1^5$-Cyclopropyl-10-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-$1^4$,$2^4$-Difluoro-$2^6$-methyl-11-oxo-10-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-$2^4$-Cyclopentyl-$1^5$-cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-$1^5$-Cyclopropyl-10-(5-(3-(diethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$1^4$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-1$^4$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-1$^5$,2$^4$-Dicyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((9*S*,12*S*)-1$^5$,2$^4$-Dicyclopropyl-9-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-10-oxo-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid;

2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^5$,2$^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((9*S*,12*S*)-1$^5$-Cyclopropyl-9-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^4$,2$^5$,2$^6$-trimethyl-10-oxo-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^6$,2$^4$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-1$^5$-Cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-11-oxo-2$^4$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((9*S*,12*S*)-1$^5$-Cyclopropyl-9-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-2$^6$-methyl-10-oxo-2$^4$-(trifluoromethyl)-3-oxa-11-aza-1(1,3),2(1,2)-dibenzenacyclododecaphane-12-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-1$^4$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-1$^4$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$,$2^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$,$2^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-$1^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-$2^4$-fluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-$1^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^5$-cyclopropyl-$1^4$-fluoro-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6S)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-$2^4$-fluoro-6-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-$1^5$-Cyclopropyl-$1^4$-fluoro-10-(4-methoxy-2-oxopyridin-1(2*H*)-yl)-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-$1^4$,$2^4$-difluoro-6-(5-(3-(3-fluoroazetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$,$2^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$,$2^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-$1^4$,$2^4$-difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-$1^4$,$2^4$-difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$2^4$-fluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-$1^5$-cyclopropyl-$1^4$-fluoro-10-(4-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^4$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-6-(4-methyl-2-oxopyridin-1(2*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^4$-Chloro-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(4-cyclopropyl-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(4-cyclopropyl-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(3-(dimethylamino)propyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$,2$^4$-trifluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-2$^4$-fluoro-6-(5-(3-(3-fluoroazetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(3-(Azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^5$-cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^2$,2$^4$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-1$^6$-Chloro-2$^5$-cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-2$^4$-fluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$-fluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(3-(Azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^4$-fluoro-$1^4$,$1^6$,$2^5$-trimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphan-8-en-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(4-(Difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$,$2^5$-trifluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Chloro-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Azetidin-1-yl)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-$1^4$,$2^4$-Difluoro-$1^5$,$2^6$-dimethyl-11-oxo-10-(3-oxo-2-azaspiro[4.5]decan-2-yl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-$1^5$-Cyclopropyl-10-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$2^3$,$2^4$,$2^6$-trimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$-trifluoro-$2^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$-fluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^2$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-$1^5$-Cyclopropyl-10-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^3$,$2^4$-trifluoro-$2^6$-methyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,8-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,8-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^6$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-$1^4$,$2^4$-Difluoro-$1^5$,$2^6$-dimethyl-10-(3-methyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-6-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(3-(Azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$,$2^5$-tetrafluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$,$2^5$-tetrafluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclododecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-$1^6$-methyl-5-oxo-6-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-$1^6$-methyl-5-oxo-6-(3-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-$1^6$,$2^5$-dimethyl-5-oxo-6-(3-oxo-2-azaspiro[4.5]decan-2-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,9-dimethyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-$1^4$,$1^6$,$2^4$-trifluoro-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$1^4$,$2^4$,$2^5$-Trifluoro-$1^6$-methyl-5-oxo-6-(3-oxo-2-azaspiro[4.5]decan-2-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-10-(4,4-Dimethyl-2-oxopyrrolidin-1-yl)-$1^4$,$2^4$-difluoro-$1^5$,$2^6$-dimethyl-11-oxo-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-$1^6$-methyl-5-oxo-6-(3-oxo-2-azaspiro[4.4]nonan-2-yl)-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-6-(3-oxo-2,8-diazaspiro[4.5]decan-2-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-6-(8-methyl-3-oxo-2,8-diazaspiro[4.5]decan-2-yl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-Bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$,2$^5$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-1$^6$-methyl-5-oxo-6-(3-oxo-8-oxa-2-azaspiro[4.5]decan-2-yl)-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-ethyl-1$^4$,2$^4$-difluoro-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(3-(Dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,1$^6$,2$^4$-trifluoro-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-1$^4$,2$^4$,2$^5$-Trifluoro-1$^6$-methyl-6-(1-methyl-2-oxo-1,3-diazaspiro[4.5]decan-3-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-2$^4$-fluoro-1$^4$,1$^6$-dimethyl-5-oxo-6-(2-oxo-5-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-12-oxa-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-2$^6$,7-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((10*S*,13*S*)-10-(5-(2-(Dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-2$^6$,4-dimethyl-11-oxo-1$^5$-(trifluoromethyl)-3-oxa-12-aza-1(1,3),2(1,2)-dibenzenacyclotridecaphane-13-yl)acetic acid;

2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-1$^6$-methyl-6-(5-(2-morpholinoethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-$1^4$,$2^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$2^5$-cyclopropyl-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$1^4$,$2^4$-Difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$,$2^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-6-(3-(3-(dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(3-(3-(Azetidin-1-yl)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^4$,$2^4$-difluoro-$1^6$-methyl-5-oxo-$2^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-$2^5$-Cyclopropyl-$1^4$,$2^4$-difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-$1^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(5-(3-hydroxypropyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-1$^4$,1$^6$,2$^4$-Trifluoro-6-(5-(2-morpholinoethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(3-(2-(Dimethylamino)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,2$^4$-difluoro-6-(3-(2-(3-fluoroazetidin-1-yl)ethyl)-5-methyl-6-oxopyridazin-1(6*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-1$^4$,2$^4$-Difluoro-6-(3-(2-(3-methoxyazetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-1$^4$,1$^6$,2$^4$-trifluoro-6-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(3-(3-(Dimethylamino)propyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$,2$^5$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-1$^3$,1$^4$,2$^4$-trifluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-2$^5$-(trifluoromethyl)-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(3-(2-(dimethylamino)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,1$^6$,2$^4$-trifluoro-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(3-(2-(Azetidin-1-yl)ethyl)-6-oxo-4-(trifluoromethyl)pyridazin-1(6*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$,2$^5$-dimethyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-2$^5$-Cyclopropyl-6-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyrimidin-1(2*H*)-yl)-1$^4$,2$^4$-difluoro-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid;

2-((3*S*,6*S*)-6-(5-(2-(3-Methoxyazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid; and
2-((3*S*,6*S*)-6-(5-(2-(3-Fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-1$^6$-methyl-5-oxo-4-aza-1(1,2),2(1,3)-dibenzenacyclotridecaphane-3-yl)acetic acid.

26. A pharmaceutical composition comprising a compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

27. A compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 26, for use in therapy.

28. A compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 26, for use in the treatment of diseases or disorders mediated by α4β7.

29. A compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 26, for use in the treatment of inflammatory bowel diseases, such as ulcerative colitis or Crohn's disease.

30. A method of treating a disease or disorders mediated by α4β7, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 26.

31. A method of treating inflammatory bowel diseases, such as ulcerative colitis or Crohn's disease, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 26.