



(86) Date de dépôt PCT/PCT Filing Date: 2018/02/05
(87) Date publication PCT/PCT Publication Date: 2018/08/09
(45) Date de délivrance/Issue Date: 2022/08/23
(85) Entrée phase nationale/National Entry: 2019/07/25
(86) N° demande PCT/PCT Application No.: US 2018/016893
(87) N° publication PCT/PCT Publication No.: 2018/145021
(30) Priorité/Priority: 2017/02/06 (US62/455,348)

(51) Cl.Int./Int.Cl. *C07D 487/08* (2006.01),
A61K 31/4439 (2006.01), *A61K 31/506* (2006.01),
A61K 31/5365 (2006.01), *A61P 31/18* (2006.01),
C07D 405/14 (2006.01), *C07D 498/04* (2006.01)

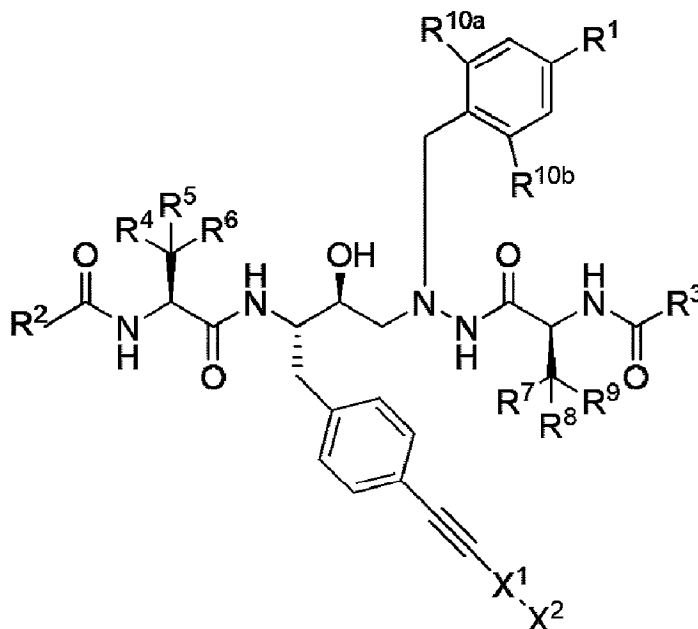
(72) Inventeurs/Inventors:
BACON, ELIZABETH M., US;
CHIN, ELBERT, US;
COTTELL, JEROMY J., US;
KATANA, ASHLEY ANNE, US;
KATO, DARRYL, US;
...

(73) Propriétaire/Owner:
GILEAD SCIENCES, INC., US

(74) Agent: ROBIC

(54) Titre : INHIBITEURS DE LA PROTEASE DU VIH

(54) Title: HIV PROTEASE INHIBITORS



(Ia)

(57) Abrégé/Abstract:

The invention provides a compound of Formula I: or a pharmaceutically acceptable salt thereof as described herein. The invention also provides pharmaceutical compositions comprising a compound of Formula I, processes for preparing compounds of Formula

(72) **Inventeurs(suite)/Inventors(continued):** LINK, JOHN O., US; SHAPIRO, NATHAN, US;
TREJO MARTIN, TERESA ALEJANDRA, US; YANG, ZHENG-YU, US

(57) **Abrégé(suite)/Abstract(continued):**

I, the compound of formula (I) for use in therapeutic methods for treating the proliferation of the HIV virus, treating AIDS or delaying the onset of AIDS symptoms in a mammal using compounds of Formula I. Preferred compounds are N-[(2S) -1-[2-[(2S,3S)-2-hydroxy-3-[[[(2S)-2-(methoxycarbonylamino) -3,3-dimethylbutanoyl]amino]-4-phenylbutyl]-2-[(phenyl methyl]hydrazinyl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate atazanavir (ATV) analogues substituted by several heterocycles, such as e.g. pyrazole (R1); e.g. oxetane (substituent of X2); e.g. pyridine or pyrimidine (X1); e.g. piperazine or 3,8-diazabicyclo[3.2.1]octan (X2).

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

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

09 August 2018 (09.08.2018)



(10) International Publication Number

WO 2018/145021 A1

(51) International Patent Classification:

C07D 403/12 (2006.01) **C07C 243/28** (2006.01)
C07D 405/14 (2006.01) **A61K 31/495** (2006.01)
C07C 275/16 (2006.01) **A61K 31/504** (2006.01)
C07D 401/12 (2006.01) **A61K 31/506** (2006.01)
C07D 471/08 (2006.01) **A61K 31/5365** (2006.01)
C07D 487/08 (2006.01) **A61K 31/4155** (2006.01)
C07D 487/10 (2006.01) **A61K 31/337** (2006.01)
C07D 491/04 (2006.01)

(21) International Application Number:

PCT/US2018/016893

(22) International Filing Date:

05 February 2018 (05.02.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/455,348 06 February 2017 (06.02.2017) US

(71) **Applicant:** GILEAD SCIENCES, INC. [US/US]; 333 Lakeside Drive, Foster City, CA 94404 (US).

(72) **Inventors:** BACON, Elizabeth M.; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). CHIN, Elbert; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). COTTELL, Jeromy J.; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). KATANA, Ashley Anne; 6599 Nancy Drive, North Olmsted, OH 44070 (US). KATO, Darryl; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA

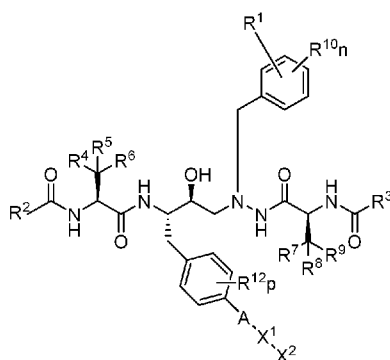
94404 (US). LINK, John O.; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). SHAPIRO, Nathan; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). TREJO MARTIN, Teresa Alejandra; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). YANG, Zheng-Yu; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US).

(74) **Agent:** LECHNER, Jolie D. et al.; Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US).

(81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(54) Title: ATAZANAVIR (ATV) ANALOGUES FOR TREATING HIV INFECTIONS



(1)

(57) **Abstract:** The invention provides a compound of Formula I: or a pharmaceutically acceptable salt thereof as described herein. The invention also provides pharmaceutical compositions comprising a compound of Formula I, processes for preparing compounds of Formula I, the compound of formula (I) for use in therapeutic methods for treating the proliferation of the HIV virus, treating AIDS or delaying the onset of AIDS symptoms in a mammal using compounds of Formula I. Preferred compounds are N-[(2S)-1-[2-[(2S,3S)-2-hydroxy-3-[[[(2S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoyl]amino]-4-phenylbutyl]-2-[(phenyl)methyl]hydrazinyl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate atazanavir (ATV) analogues substituted by several heterocycles, such as e.g. pyrazole (R1); e.g. oxetane (substituent of X2); e.g. pyridine or pyrimidine (X1); e.g. piperazine or 3,8-diazabicyclo[3.2.1]octan (X2).

[Continued on next page]



WO 2018/145021 A1

WO 2018/145021 A1

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

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

Published:

- *with international search report (Art. 21(3))*

HIV PROTEASE INHIBITORS

FIELD

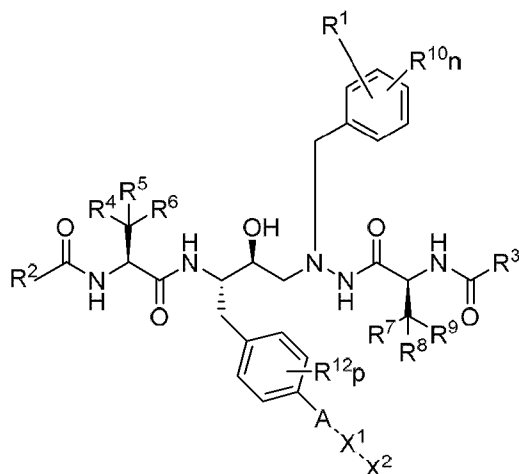
5 The present disclosure relates to novel compounds for use in the treatment of a *Retroviridae* viral infection including an infection caused by the HIV virus. The present disclosure also relates to intermediates for its preparation and to pharmaceutical compositions containing those compounds.

BACKGROUND

10 Human immunodeficiency virus (HIV) infection and related diseases are a major public health problem worldwide. Human immunodeficiency virus type 1 (HIV-1) encodes three enzymes which are required for viral replication: reverse transcriptase, protease, and integrase. Several protease inhibitors (PI) are presently approved for use in AIDS or HIV. Yet many PI inhibitors suffer from high rates of hepatic metabolism, which may require co-administration of a
15 booster or more frequent dosing. Furthermore, viral resistance remains a problem. Accordingly, there is a need for new agents that inhibit the replication of HIV.

SUMMARY

 The present disclosure provides compounds and methods for the treatment of an HIV infection. Accordingly, in one embodiment, the invention provides a compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a 5 to 10-membered heterocycle having 1 to 5 heteroatoms selected from N, O, and S, or a 5 to 10-membered heteroaryl having 1 to 5 heteroatoms selected from N, O, and S, wherein the 5 to 10-membered heterocycle or 5 to 10-membered heteroaryl is optionally

5 substituted with 1 to 5 R^a groups;

R^2 and R^3 are each independently C_{1-4} alkyl, C_{3-6} cycloalkyl, $O-R^{2A}$, C_{1-2} alkyl- $O-R^{2A}$, $N-(R^{3A})_2$, or C_{1-2} alkyl- $N-(R^{3A})_2$,

wherein each R^{2A} is independently C_{1-4} alkyl, C_{3-6} cycloalkyl, or a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S,

10 wherein each R^{3A} is independently hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, or $COO(R^e)$,

and wherein each C_{3-6} cycloalkyl or 4 to 10-membered heterocyclyl is optionally substituted by 1 to 3 R^f groups, wherein each R^f is independently C_{1-2} alkyl or halogen;

R^4 is hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, or C_{1-4} haloalkoxy;

R^7 is hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, or C_{1-4} haloalkoxy;

15 R^5 , R^6 , R^8 , and R^9 are each independently hydrogen, halo, C_{1-2} alkyl, C_{1-2} haloalkyl, or C_{3-6} cycloalkyl;

and wherein two or more of R^4 , R^5 and R^6 or two or more of R^7 , R^8 , and R^9 optionally join together to form one or more C_{3-6} cycloalkyl groups that are optionally substituted with 1 to 4 groups selected from halogen, C_{1-2} alkyl, and C_{1-2} haloalkyl;

20 each R^{10} is independently halogen, cyano, C_{1-4} alkoxy, C_{1-6} alkyl, or C_{3-6} cycloalkyl;

n is 0 to 4;

each R^a is independently halogen, C_{1-4} alkyl, C_{1-4} alkyl with 1 to 2 groups selected from hydroxyl and C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, 4 to 10-membered

25 heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S which is optionally substituted with R^{a1} , or $O-R^{3B}$,

wherein R^{3B} is C_{3-6} cycloalkyl optionally substituted with R^{a1} or a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S optionally substituted with R^{a1} ,

30 wherein each R^{a1} is independently C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or 4 to 8-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S;

A is ethynyl or a bond;

X^1 is a 6 to 10-membered aryl or a 5 to 10-membered heteroaryl having 1 to 3 heteroatoms selected from N, O, and S, wherein each 6 to 10-membered aryl or 5 to 10-membered heteroaryl is optionally substituted with 1 to 4 R^b groups;

X^2 is hydrogen or a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S, wherein the 4 to 10-membered heterocyclyl is optionally substituted with one R^{11} and optionally substituted with 1 to 5 R^b groups;

R^{11} is $C=O(R^c)$, $CH_2(R^d)$, $S(O)_{1-2}(C_{1-4}alkyl)$, $S(O)_{1-2}C_{3-6}cycloalkyl$, a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S, or a 5 to 9-membered heteroaryl having 1 to 5 heteroatoms selected from N, O, and S, wherein each 4 to 10-membered heterocyclyl or 5 to 9-membered heteroaryl is optionally substituted with 1 to 5 R^b groups;

each R^b is independently halogen, oxo, $C_{1-4}alkyl$, $C_{1-4}alkyl$ with 1 to 2 groups selected from hydroxyl and $C_{1-4}alkoxy$, $C_{1-4}haloalkyl$, $C_{1-4}alkoxy$, or $COO(R^e)$;

R^c is $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, $C_{1-4}alkoxy$, $N(R^e)_2$, $C_{3-6}cycloalkyl$, or a 4 to 6-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S, wherein the $C_{3-6}cycloalkyl$ and the 4 to 6-membered heterocyclyl are optionally substituted by 1 to 5 R^b groups;

R^d is $COO(R^e)$, $N(R^e)_2$, $C_{3-6}cycloalkyl$, or a 4 to 6-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S, wherein the $C_{3-6}cycloalkyl$ and the 4 to 6-membered heterocyclyl is optionally substituted by 1 to 5 R^b groups;

each R^{12} is $C_{1-2}alkyl$, halo, $-OC_{1-2}alkyl$, or cyano;

each p is 0 to 4;

and each R^e is independently hydrogen or $C_{1-4}alkyl$.

Also provided is a pharmaceutical composition comprising a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition further comprising one, two, three, or four additional therapeutic agents.

Also provided is method of treating or preventing a human immunodeficiency virus (HIV) infection comprising administering a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

In certain embodiments, the current disclosure relates to an article of manufacture comprising a unit dosage of a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

Also provided is a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

A compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in a method of treating or preventing a human immunodeficiency virus (HIV) infection comprising
 5 administering a therapeutically effective amount of said compound to a subject in need thereof, is also provided.

DESCRIPTION OF THE DRAWINGS

Figure 1 describes the hepatic predicted clearance for certain compounds and reference compounds as more fully described in the biological examples herein.

10 **Figure 2** describes a graph of the IV dog pharmacokinetic studies for certain compounds and reference compounds and table summarizing IV and oral PK data for those compounds as more fully described in the examples herein.

Figure 3 describes a graph of the IV rat pharmacokinetic studies for certain compounds and reference compounds and table summarizing IV and oral PK data for those compounds as more
 15 fully described in the examples herein.

Figure 4 describes the fold change vs. wild type for certain clinical isolate resistance mutations for certain compounds and reference compounds as more fully described in the examples herein.

Figure 5 describes the resistance breakthrough for certain compounds and reference compounds as more fully described in the examples herein.

20 DETAILED DESCRIPTION

The following is a list of abbreviations and acronyms used throughout the application:

Abbreviation	Meaning
°C	Degree Celsius
ATP	Adenosine-5'-triphosphate
AcOH	Acetic acid
d	Doublet
dd	Doublet of doublets
DCE	1,2-dichloroethane
DCM	Dichloromethane
DIPEA	N,N-diisopropylethylamine
DME	1,2-dimethoxyethane

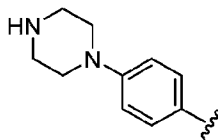
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EGTA	Ethylene glycol tetraacetic acid
ETOAC	Ethyl acetate
equiv/eq	Equivalents
ESI	Electrospray ionization
Ac	Acetate
Et	Ethyl
g	Grams
HATU	2-(7-Aza-1H-Benzotriazole -1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
hERG	human Ether-à-go-go Related Gene
HPLC	High-performance liquid chromatography
h/hr	Hours
Hz	Hertz
IC ₅₀	The half maximal inhibitory concentration
J	Coupling constant
Kg	Kilogram
M	Molar
m	multiplet
m/z	mass-to-charge ratio
M+	Mass peak
M+H	Mass peak plus hydrogen
Me	Methyl
MeOH	Methyl alcohol/methanol
mg	Milligram
MHz	Megahertz
min/m	Minute
ml/mL	Milliliter
mM	Millimolar
mmol	Millimole
MS	Mass spectroscopy

mw	Microwave
N	Normal
mol	Mole
NMP	<i>N</i> -methylpyrrolidinone
NMR	Nuclear magnetic resonance
Ph	Phenyl
ppm	Parts per million
prep	Preparative
R _f	Retention factor
RP	Reverse phase
RT/rt	Room temperature
s	Second
s	Singlet
t	Triplet
TEA	Triethylamine
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TMS	trimethylsilyl
WT	Wild type
δ	Chemical shift
μg	Microgram
μL/ μl	Microliter
μM	Micromolar
μm	Micrometer
μmol	Micromole

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. It must be noted that as used herein and in the appended claims, the singular forms “a”, “and”, and “the” include plural referents unless the context clearly dictates otherwise. Thus, e.g., reference to “the compound” includes a plurality of such compounds and reference to “the assay” includes reference to one or more assays and equivalents thereof known to those skilled in the art, and so forth.

A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary

meaning. A wavy line drawn through a line in a structure indicates a point of attachment of a group, e.g.:



A dashed line indicates an optional bond. Where multiple substituent groups are identified the point of attachment is at the terminal substituent (e.g. for “alkylaminocarbonyl” the point of attachment is at the carbonyl substituent).

The prefix “C_{x-y}” indicates that the following group has from x (e.g. 1) to y (e.g. 6) carbon atoms, one or more of which, in certain groups (e.g. heteroalkyl, heteroaryl, heteroarylalkyl, etc), may be replaced with one or more heteroatoms or heteroatomic groups.

For example, “C₁₋₆ alkyl” indicates that the alkyl group has from 1 to 6 carbon atoms. Likewise, the term “x-y membered” rings, wherein x and y are numerical ranges, such as “3 to 12-membered heterocyclyl”, refers to a ring containing x-y atoms (e.g. 3-12), of which up to 80% may be heteroatoms, such as N, O, S, P, and the remaining atoms are carbon.

Also, certain commonly used alternative chemical names may or may not be used. For example, a divalent group such as a divalent “alkyl” group, a divalent “aryl” group, etc., may also be referred to as an “alkylene” group or an “alkylenyl” group, or alkyl group, an “arylene” group or an “arylenyl” group, or aryl group, respectively.

“A compound disclosed herein” or “a compound of the present disclosure” refers to the compounds of Formula (I), (Ia), (Ib), (Ic), (Id), and/or (Ie). Also included are the specific compounds of Examples 1-245.

“Alkyl” refers to any group derived from a linear or branched saturated hydrocarbon. Alkyl groups include, but are not limited to, methyl, ethyl, propyl such as propan-1-yl, propan-2-yl (isopropyl), butyls such as butan-1-yl, butan-2-yl (sec-butyl), 2-methyl-propan-1-yl (iso-butyl), 2-methyl-propan-2-yl (t-butyl), pentyls, hexyls, octyls, decyls, and the like. Unless otherwise specified, an alkyl group has from 1 to 10 carbon atoms, for example from 1 to 6 carbon atoms, for example from 1 to 4 carbon atoms.

“Alkenyl” refers to any group derived from a straight or branched hydrocarbon with at least one carbon-carbon double bond. Alkenyl groups include, but are not limited to, ethenyl (vinyl), propenyl (allyl), 1-butenyl, 1,3-butadienyl, and the like. Unless otherwise specified, an

alkenyl group has from 2 to 10 carbon atoms, for example from 2 to 6 carbon atoms, for example from 2 to 4 carbon atoms.

“Alkynyl” refers to any group derived from a straight or branched hydrocarbon with at least one carbon-carbon triple bond and includes those groups having one triple bond and one double bond. Examples of alkynyl groups include, but are not limited to, ethynyl ($\text{-C}\equiv\text{C-}$), propargyl ($\text{-CH}_2\text{C}\equiv\text{C-}$), (*E*)-pent-3-en-1-ynyl, and the like. Unless otherwise specified, an alkynyl group has from 2 to 10 carbon atoms, for example from 2 to 6 carbon atoms, for example from 2 to 4 carbon atoms.

“Amino” refers to -NH_2 . Amino groups may also be substituted as described herein, such as with alkyl, carbonyl or other amino groups. The term “alkylamino” refers to an amino group substituted with one or two alkyl substituents (e.g. dimethylamino or propylamino).

The term “aryl” as used herein refers to a single all carbon aromatic ring or a multiple condensed all carbon ring system wherein at least one of the rings is aromatic. For example, in certain embodiments, an aryl group has 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 12 carbon atoms. Aryl includes a phenyl radical. Aryl also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) having about 9 to 20 carbon atoms in which at least one ring is aromatic and wherein the other rings may be aromatic or not aromatic (i.e., carbocycle). Such multiple condensed ring systems are optionally substituted with one or more (e.g., 1, 2 or 3) oxo groups on any carbocycle portion of the multiple condensed ring system. The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. It is also to be understood that when reference is made to a certain atom-range membered aryl (e.g., 6-10 membered aryl), the atom range is for the total ring atoms of the aryl. For example, a 6-membered aryl would include phenyl and a 10-membered aryl would include naphthyl and 1, 2, 3, 4-tetrahydronaphthyl. Aryl groups include, but are not limited to, those groups derived from acenaphthylene, anthracene, azulene, benzene, chrysene, a cyclopentadienyl anion, naphthalene, fluoranthene, fluorene, indane, perylene, phenalene, phenanthrene, pyrene and the like. Non-limiting examples of aryl groups include, but are not limited to, phenyl, indenyl, naphthyl, 1, 2, 3, 4-tetrahydronaphthyl, anthracenyl, and the like.

“Bridged” refers to a ring fusion wherein non-adjacent atoms on a ring are joined by a divalent substituent, such as an alkylene or heteroalkylene group or a single heteroatom. Quinuclidinyl and adamantanyl are examples of bridged ring systems.

The term “cycloalkyl” refers to a single saturated or partially unsaturated all carbon ring having 3 to 20 annular carbon atoms (i.e., C₃₋₂₀ cycloalkyl), for example from 3 to 12 annular atoms, for example from 3 to 10 annular atoms. The term “cycloalkyl” also includes multiple condensed, saturated and partially unsaturated all carbon ring systems (e.g., ring systems comprising 2, 3 or 4 carbocyclic rings). Accordingly, cycloalkyl includes multicyclic carbocycles such as a bicyclic carbocycles (e.g., bicyclic carbocycles having about 6 to 12 annular carbon atoms such as bicyclo[3.1.0]hexane and bicyclo[2.1.1]hexane), and polycyclic carbocycles (e.g. tricyclic and tetracyclic carbocycles with up to about 20 annular carbon atoms). The rings of a multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. Non-limiting examples of monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, spiro[3.3]heptane, and 1-cyclohex-3-enyl.

“Halo” and “halogen” refer to fluoro, chloro, bromo and iodo.

“Haloalkyl” refers to an alkyl wherein one or more hydrogen atoms are each replaced by a halogen. Examples include, but are not limited to, -CH₂Cl, -CH₂F, -CH₂Br, -CFCIBr, -CH₂CH₂Cl, -CH₂CH₂F, -CF₃, -CH₂CF₃, -CH₂CCl₃, and the like, as well as alkyl groups such as perfluoroalkyl in which all hydrogen atoms are replaced by fluorine atoms.

“Alkoxy” or “alkoxyl” refers to a moiety of the formula -O-alkyl, wherein the alkyl portion is as defined above. For example, C₁₋₄ alkoxy refers to a moiety having 1-4 carbon alkyl group attached to the oxygen. “Haloalkoxy” or “haloalkoxyl” refers to a moiety of the formula -O-haloalkyl, wherein the haloalkyl portion is as defined above. For example, C₁₋₄ alkoxy refers to a moiety having 1-4 carbon halo alkyl group attached to the oxygen.

“Heteroalkyl” refers to an alkyl in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatom or heteroatomic ngroup. Heteroatoms include, but are not limited to, N, P, O, S, etc. Heteroatomic groups include, but are not limited to, -NR-, -O-, -S-, -PH-, -P(O)₂-, -S(O)-, -S(O)₂-, and the like, where R is H, alkyl, aryl, cycloalkyl, heteroalkyl, heteroaryl or cycloheteroalkyl. Heteroalkyl groups include, but are not limited to, -OCH₃, -CH₂OCH₃, -SCH₃, -CH₂SCH₃, -NRCH₃, -CH₂NRCH₃, -CH₂OH and the like, where R is hydrogen, alkyl, aryl, arylalkyl, heteroalkyl, or heteroaryl, each of which may be optionally substituted. A heteroalkyl group comprises from 1 to 10 carbon and up to four three hetero atoms, e.g., from 1

to 6 carbon and from 1 to 2 hetero atoms.

“Heteroaryl” refers to mono or multicyclic aryl group in which one or more of the aromatic carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatom or heteroatomic group, as defined above. Multicyclic ring systems are included in heteroaryl and may be attached at the ring with the heteroatom or the aryl ring. Heteroaryl groups include, but are not limited to, groups derived from acridine, benzoimidazole, benzothiophene, benzofuran, benzoxazole, benzothiazole, carbazole, carboline, cinnoline, furan, imidazole, imidazopyridine, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyridone, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like. Heteroaryl groups may have 5-12 members, 5-10 members, or 5-6 members.

The term “heterocyclyl” or “heterocycle” as used herein refers to a single saturated or partially unsaturated non-aromatic ring or a non-aromatic multiple ring system that has at least one heteroatom in the ring (i.e., at least one annular heteroatom selected from oxygen, nitrogen, and sulfur). Unless otherwise specified, a heterocyclyl group has from 5 to about 20 annular atoms, for example from 3 to 12 annular atoms, for example from 3 to 10 annular atoms, for example from 5 to 10 annular atoms or for example from 5 to 6 annular atoms. Thus, the term includes single saturated or partially unsaturated rings (e.g., 3, 4, 5, 6 or 7-membered rings) having from about 1 to 6 annular carbon atoms and from about 1 to 3 annular heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the ring. The rings of the multiple condensed ring (e.g. bicyclic heterocyclyl) system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. Heterocycles include, but are not limited to, groups derived from azetidine, aziridine, imidazolidine, morpholine, oxirane (epoxide), oxetane, piperazine, piperidine, pyrazolidine, piperidine, pyrrolidine, pyrrolidinone, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, tetrahydro-2H-thiopyran 1,1-dioxide, quinuclidine, N-bromopyrrolidine, N-chloropiperidine, and the like. Heterocycles include spirocycles, such as, for example, aza or oxo-spiroheptanes. Heterocyclyl groups also include partially unsaturated ring systems containing one or more double bonds, including fused ring systems with one aromatic ring and one non-aromatic ring, but not fully aromatic ring systems. Examples include dihydroquinolines, e.g. 3,4-dihydroquinoline, dihydroisoquinolines, e.g. 1,2-dihydroisoquinoline, dihydroimidazole,

tetrahydroimidazole, etc., indoline, isoindoline, isoindolones (e.g. isoindolin-1-one), isatin, dihydrophthalazine, quinolinone, spiro[cyclopropane-1,1'-isoindolin]-3'-one, and the like.

Additional examples of heterocycles include 3,8-diazabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 3,6-diazabicyclo[3.1.1]heptanyl, 3-oxa-7,9-

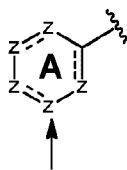
5 diazabicyclo[3.3.1]nonanyl, and hexahydropyrazino[2,1-c][1,4]oxaziny, for example.

“Hydroxyl” and “hydroxy” are used interchangeably and refer to $-OH$. “Oxo” refers to =O or —O^- . Where tautomeric forms of the compound exist, hydroxyl and oxo groups are interchangeable.

It is understood that combinations of chemical groups may be used and will be
 10 recognized by persons of ordinary skill in the art. For instance, the group “hydroxyalkyl” would refer to a hydroxyl group attached to an alkyl group. A great number of such combinations may be readily envisaged. Additional examples of substituent combinations used herein include: C_{1-6} alkylamincarbonyl (e.g. $CH_3CH_2NHC(O)-$), C_{1-6} alkoxy carbonyl (e.g. $CH_3O-C(O)-$), 5-7 membered heterocyclyl- C_{1-6} alkyl (e.g. piperazinyl- CH_2-), C_{1-6} alkylsulfonyl-5-7 membered
 15 heterocyclyl (e.g. $CH_3S(O)_2$ -morpholinyl-), 5-7 membered heterocyclyl C_{1-6} alkoxy 5-7 membered heterocyclyloxy, (4-7 membered heterocyclyl)-4-7 membered heterocyclyl (e.g. oxetanyl-pyrrolidinyl-), C_{3-6} cycloalkylaminocarbonyl (e.g. cyclopropyl- $NH-C(O)-$), 5-7 membered heterocyclyl- C_{2-6} alkynyl (e.g. N-piperazinyl- $CH_2C\equiv CCH_2-$), and C_{6-10} arylaminocarbonyl (e.g. phenyl- $NH-C(O)-$).

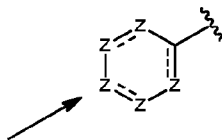
20 “Spiro” refers to a ring substituent which is joined by two bonds at the same carbon atom. Examples of spiro groups include 1,1-diethylcyclopentane, dimethyl-dioxolane, and 4-benzyl-4-methylpiperidine, wherein the cyclopentane and piperidine, respectively, are the spiro substituents. When substituents (R-groups) join together (e.g. when R^7 and R^8 join together) they may be taken from the same point of attachment to form a spiro ring.

25 The phrase “*meta* (3) position with respect to the point of attachment of the A ring”, refers to the position on the ring where the substituent (e.g. $-CN$) is adjoined and is shown below with an arrow, wherein z represents a carbon atom or nitrogen:

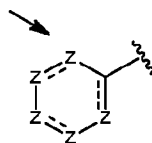


Similarly, *para* (4) position substitution refers to attachment of a substituent at the

position indicated below, with respect to the point of attachment (e.g. of the B ring):



Similarly, *ortho* or 2-position refers to attachment of a substituent at the position indicated below, with respect to the point of attachment:



5

The compounds described herein include isomers, stereoisomers and the like. As used herein, the term "isomers" refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term "a stereoisomer" refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound.

The term "fused" refers to a ring which is bound to an adjacent ring.

"Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture.

The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent

may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included. To the extent that compounds depicted herein are represented as having a particular stereochemistry, it is understood by one of skill in the art that such compounds may contain
5 some detectable or undetectable levels of compounds sharing the same structure, but having different stereochemistry.

“IC₉₅” or “EC₉₅” refers to the inhibitory concentration required to achieve 95% of the maximum desired effect, which in many cases here is the inhibition of the HIV virus. This term is obtained using an *in vitro* assay evaluating the concentration-dependent inhibition of wild type
10 HIV virus.

“IC₅₀” or “EC₅₀” refers to the inhibitory concentration required to achieve 50% of the maximum desired effect, which in many cases here is the inhibition of the HIV virus. This term is obtained using an *in vitro* assay evaluating the concentration-dependent inhibition of wild type HIV virus.

15 “IQ” or “inhibitory quotient” refers to the ratio between the trough drug concentration (C_{tau}) and level of drug resistance of the HIV isolate as determined by the IC₉₅ (i.e. C_{tau}/IC₉₅).

“Pharmaceutically acceptable” refers to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

20 “Pharmaceutically acceptable excipient” includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

25 “Pharmaceutically acceptable salt” refers to a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid,
30 benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, lactic acid, maleic acid, malonic acid, mandelic acid, methanesulfonic acid, 2-naphthalenesulfonic acid, oleic acid, palmitic acid, propionic

acid, stearic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, trimethylacetic acid, and the like, and salts formed when an acidic proton present in the parent compound is replaced by either a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as diethanolamine, triethanolamine, N-methylglucamine and the like. Also included in this definition are ammonium and substituted or quaternized ammonium salts. Representative non-limiting lists of pharmaceutically acceptable salts can be found in S.M. Berge et al., J. Pharma Sci., 66(1), 1-19 (1977), and Remington: The Science and Practice of Pharmacy, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, PA, (2005), at p. 732, Table 38-5.

The present disclosure also provides for prodrugs of the compounds disclosed herein. A “prodrug” is defined in the pharmaceutical field as a biologically inactive derivative of a drug that upon administration to the human body is converted to the biologically active parent drug according to some chemical or enzymatic pathway.

“Subject” and “subjects” refers to humans, domestic animals (e.g., dogs and cats), farm animals (e.g., cattle, horses, sheep, goats and pigs), laboratory animals (e.g., mice, rats, hamsters, guinea pigs, pigs, pocket pets, rabbits, dogs, and monkeys), and the like.

As used herein, “treatment” or “treating” is an approach for obtaining beneficial or desired results. For purposes of the present disclosure, beneficial or desired results include, but are not limited to, alleviation of a symptom and/or diminishment of the extent of a symptom and/or preventing a worsening of a symptom associated with a disease or condition. In one embodiment, “treatment” or “treating” includes one or more of the following: a) inhibiting the disease or condition (e.g., decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more symptoms associated with the disease or condition (e.g., stabilizing the disease or condition, delaying the worsening or progression of the disease or condition); and/or c) relieving the disease or condition, e.g., causing the regression of clinical symptoms, ameliorating the disease state, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival.

As used herein, “delaying” development of a disease or condition means to defer, hinder, slow, retard, stabilize and/or postpone development of the disease or condition. This delay can be of varying lengths of time, depending on the history of the disease and/or subject being

treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the subject does not develop the disease or condition. For example, a method that “delays” development of AIDS is a method that reduces the probability of disease development in a given time frame and/or reduces extent of the disease in a given
5 time frame, when compared to not using the method. Such comparisons may be based on clinical studies, using a statistically significant number of subjects. For example, the development of AIDS can be detected using known methods, such as confirming a subject’s HIV⁺ status and assessing the subject’s T-cell count or other indication of AIDS development, such as extreme fatigue, weight loss, persistent diarrhea, high fever, swollen lymph nodes in the
10 neck, armpits or groin, or presence of an opportunistic condition that is known to be associated with AIDS (*e.g.*, a condition that is generally not present in subjects with functioning immune systems but does occur in AIDS patients). Development may also refer to disease progression that may be initially undetectable and includes occurrence, recurrence and onset.

As used herein, “prevention” or “preventing” refers to a regimen that protects against the
15 onset of the disease or disorder such that the clinical symptoms of the disease do not develop. Thus, “prevention” relates to administration of a therapy (*e.g.*, administration of a therapeutic substance) to a subject before signs of the disease are detectable in the subject (*e.g.*, administration of a therapeutic substance to a subject in the absence of detectable infectious agent (*e.g.*, virus) in the subject). The subject may be an individual at risk of developing the
20 disease or disorder, such as an individual who has one or more risk factors known to be associated with development or onset of the disease or disorder. Thus, the term “preventing HIV infection” refers to administering to a subject who does not have a detectable HIV infection an anti-HIV therapeutic substance. It is understood that the subject for anti-HIV preventative therapy may be an individual at risk of contracting the HIV virus. Further, it is understood that
25 prevention may not result in complete protection against onset of the disease or disorder. In some instances, prevention includes reducing the risk of developing the disease or disorder. The reduction of the risk may not result in complete elimination of the risk of developing the disease or disorder.

As used herein, an “at risk” individual is an individual who is at risk of developing a
30 condition to be treated. An individual “at risk” may or may not have detectable disease or condition, and may or may not have displayed detectable disease prior to the treatment of methods described herein. “At risk” denotes that an individual has one or more so-called risk factors, which are measurable parameters that correlate with development of a disease or

condition and are known in the art. An individual having one or more of these risk factors has a higher probability of developing the disease or condition than an individual without these risk factor(s). For example, individuals at risk for AIDS are those having HIV.

As used herein, the term "therapeutically effective amount" or "effective amount" refers to an amount that is effective to elicit the desired biological or medical response, including the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease or to an amount that is effective to protect against the contracting or onset of a disease. The effective amount will vary depending on the compound, the disease, and its severity and the age, weight, etc., of the subject to be treated. The effective amount can include a range of amounts. As is understood in the art, an effective amount may be in one or more doses, *i.e.*, a single dose or multiple doses may be required to achieve the desired treatment outcome. An effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved. Suitable doses of any co-administered compounds may optionally be lowered due to the combined action (*e.g.*, additive or synergistic effects) of the compounds.

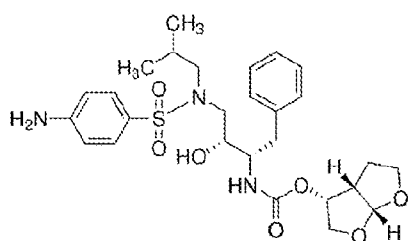
The compounds of the invention include solvates, hydrates, tautomers, stereoisomers and salt forms thereof.

Provided are also compounds in which from 1 to n hydrogen atoms attached to a carbon atom may be replaced by a deuterium atom or D, in which n is the number of hydrogen atoms in the molecule. As known in the art, the deuterium atom is a non-radioactive isotope of the hydrogen atom. Such compounds exhibit may increase resistance to metabolism, and thus may be useful for increasing the half-life of the compounds when administered to a mammal. See, *e.g.*, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," Trends Pharmacol. Sci., 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogen atoms have been replaced by deuterium.

Examples of isotopes that can be incorporated into the disclosed compounds also include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I , respectively. Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor

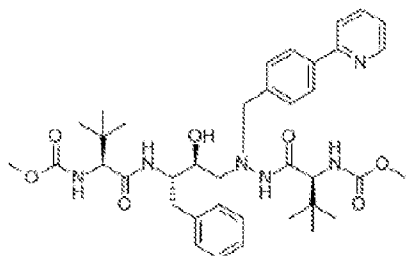
occupancy. Isotopically-labeled compounds of Formula (Ia) or (Ib), can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

- 5 As referenced herein, darunavir is a HIV protease inhibitor having the structure:



and having the IUPAC name [(3aS,4R,6aR)-2,3,3a,4,5,6a-hexahydrofuro[2,3-b]furan-4-yl] N-[(2S,3R)-4-[(4-aminophenyl)sulfonyl]-2-methylpropyl]amino]-3-hydroxy-1-phenylbutan-2-yl] carbamate. Darunavir (DRV) is marketed under the brand name PREZISTA®.

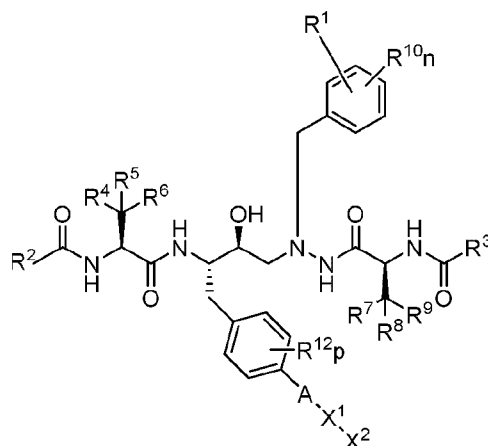
- 10 As referenced herein, atazanavir is a HIV protease inhibitor having the structure:



and having the IUPAC name methyl N-[(2S)-1-[2-[(2S,3S)-2-hydroxy-3-[(2S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoyl]amino]-4-phenylbutyl]-2-[(4-pyridin-2-yl)phenyl]methyl]hydrazinyl]-3,3-dimethyl-1-oxobutan-2-yl] carbamate. Atazanavir (ATV) is marketed under the brand name REYATAZ®.

15 **COMPOUNDS**

In certain embodiments, a compound of Formula I is provided:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is a 5 to 10-membered heterocycle having 1 to 5 heteroatoms selected from N, O, and S, or a 5 to 10-membered heteroaryl having 1 to 5 heteroatoms selected from N, O, and S,

5 wherein the 5 to 10-membered heterocycle or 5 to 10-membered heteroaryl is optionally substituted with 1 to 5 R^a groups;

R² and R³ are each independently C₁₋₄alkyl, C₃₋₆cycloalkyl, O-R^{2A}, C₁₋₂alkyl-O-R^{2A}, N-(R^{3A})₂, or C₁₋₂alkyl-N-(R^{3A})₂,

10 wherein each R^{2A} is independently C₁₋₄alkyl, C₃₋₆cycloalkyl, or a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S,

wherein each R^{3A} is independently hydrogen, C₁₋₄alkyl, C₃₋₆cycloalkyl, or COO(R^c),

and wherein each C₃₋₆cycloalkyl or 4 to 10-membered heterocyclyl is optionally substituted by 1 to 3 R^f groups, wherein each R^f is independently C₁₋₂alkyl or halogen;

R⁴ is hydrogen, halo, C₁₋₄alkyl, C₁₋₄haloalkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy, or C₁₋₄haloalkoxy;

15 R⁷ is hydrogen, halo, C₁₋₄alkyl, C₁₋₄haloalkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy, or C₁₋₄haloalkoxy;

R⁵, R⁶, R⁸, and R⁹ are each independently hydrogen, halo, C₁₋₂alkyl, C₁₋₂haloalkyl, or C₃₋₆cycloalkyl;

and wherein two or more of R⁴, R⁵ and R⁶ or two or more of R⁷, R⁸, and R⁹

optionally join together to form one or more C₃₋₆cycloalkyl groups that are

20 optionally substituted with 1 to 4 groups selected from halogen, C₁₋₂alkyl, and C₁₋₂haloalkyl;

each R¹⁰ is independently halogen, cyano, C₁₋₄alkoxy, C₁₋₆alkyl, or C₃₋₆cycloalkyl;

n is 0 to 4;

each R^a is independently halogen, C_{1-4} alkyl, C_{1-4} alkyl with 1 to 2 groups selected from hydroxyl and C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S which is optionally substituted with R^{a1} , or $O-R^{3B}$,

5 wherein R^{3B} is C_{3-6} cycloalkyl optionally substituted with R^{a1} or a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S optionally substituted with R^{a1} ,
 wherein each R^{a1} is independently C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or 4 to 8-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S;

10 A is ethynyl or a bond;

X^1 is a 6 to 10-membered aryl or a 5 to 10-membered heteroaryl having 1 to 3 heteroatoms selected from N, O, and S, wherein each 6 to 10-membered aryl or 5 to 10-membered heteroaryl is optionally substituted with 1 to 4 R^b groups;

X^2 is hydrogen or a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N,
 15 O, and S, wherein the 4 to 10-membered heterocyclyl is optionally substituted with one R^{11} and optionally substituted with 1 to 5 R^b groups;

R^{11} is $C=O(R^c)$, $CH_2(R^d)$, $S(O)_{1-2}(C_{1-4}alkyl)$, $S(O)_{1-2}C_{3-6}cycloalkyl$, a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S, or a 5 to 9-membered heteroaryl having 1 to 5 heteroatoms selected from N, O, and S, wherein each 4 to 10-membered heterocyclyl or 5 to 9-membered heteroaryl is optionally substituted with 1 to
 20 5 R^b groups;

each R^b is independently halogen, oxo, C_{1-4} alkyl, C_{1-4} alkyl with 1 to 2 groups selected from hydroxyl and C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} alkoxy, or $COO(R^e)$;

R^c is C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, $N(R^e)_2$, $C_{3-6}cycloalkyl$, or a 4 to 6-membered
 25 heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S, wherein the C_{3-6} cycloalkyl and the 4 to 6-membered heterocyclyl are optionally substituted by 1 to 5 R^b groups;

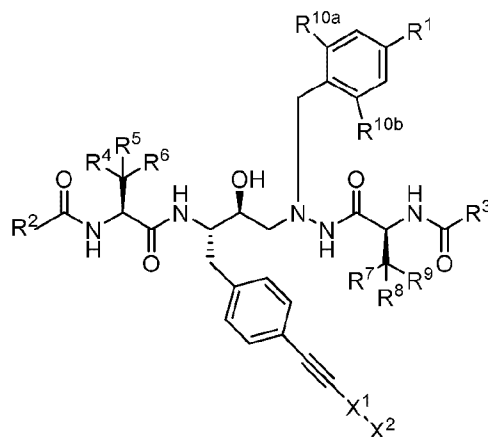
R^d is $COO(R^e)$, $N(R^e)_2$, C_{3-6} cycloalkyl, or a 4 to 6-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S, wherein the C_{3-6} cycloalkyl and the 4 to 6-membered heterocyclyl is optionally substituted by 1 to 5 R^b groups;

30 each R^{12} is C_{1-2} alkyl, halo, $-OC_{1-2}alkyl$, or cyano;

each p is 0 to 4;

and each R^e is independently hydrogen or C_{1-4} alkyl.

In certain embodiments, the compound of Formula I is a compound of Formula (Ia):

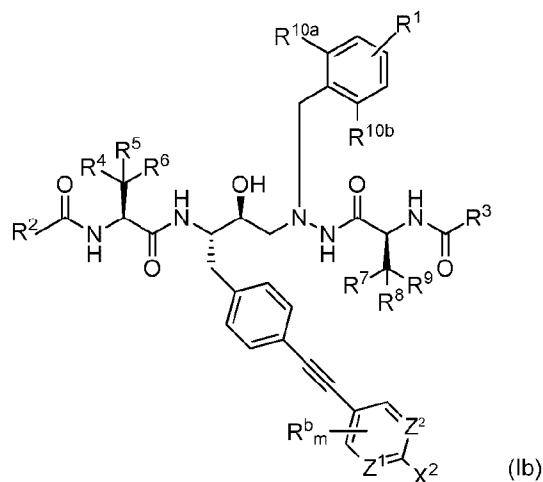


(la)

wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, X¹, and X² are as defined herein and R^{10a} and R^{10b} are independently halogen, cyano, C₁₋₄alkoxy, C₁₋₆alkyl, or C₃₋₆cycloalkyl.

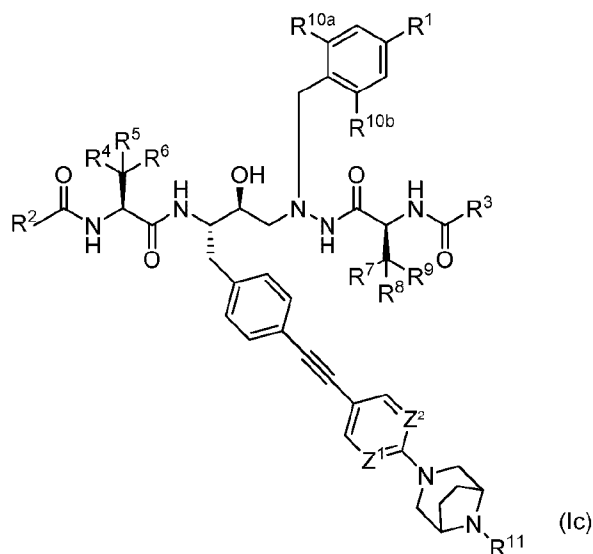
In certain embodiments, the compound of Formula I or Formula (Ia) is a compound of

5 Formula (Ib)



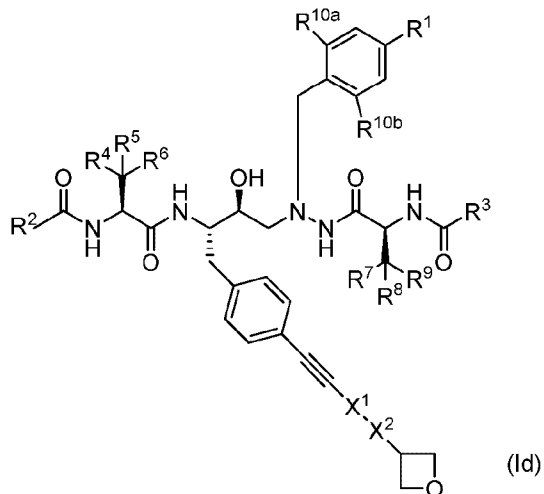
wherein: Z^1 and Z^2 are independently N or CH; m is 0 to 2, R^{10a} and R^{10b} are independently halogen, cyano, C_{1-4} alkoxy, C_{1-6} alkyl, or C_{3-6} cycloalkyl, and R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and X^2 are as defined herein.

10 In certain embodiments, the compound of Formula I, (Ia), or (Ib), is a compound of Formula (Ic):



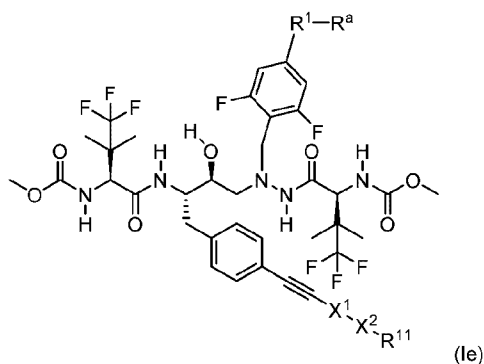
wherein Z¹ and Z² are independently N or CH, R^{10a} and R^{10b} are independently halogen, cyano, C₁₋₄alkoxy, C₁₋₆alkyl, or C₃₋₆cycloalkyl, and R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹, are as defined herein.

- 5 In certain embodiments, the compound of Formula I or (Ia) is a compound of Formula (Id):



wherein R^{10a} and R^{10b} are independently halogen, cyano, C₁₋₄alkoxy, C₁₋₆alkyl, or C₃₋₆cycloalkyl, and R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, X¹ and X² are as defined herein.

- 10 In certain embodiments,, the compound of Formula I or (Ia) is a compound of Formula (Ie):

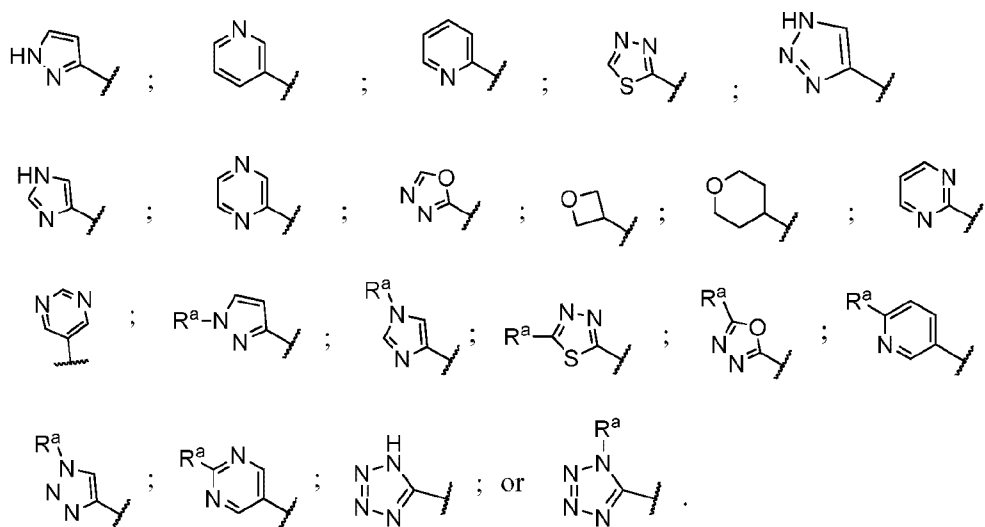


wherein R^1 , R^a , R^{11} , X^1 and X^2 are as defined herein.

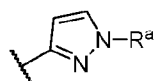
In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), R^4 and R^7 may be the same or different. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl. In certain embodiments, R^4 is C_{1-4} haloalkyl. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), R^4 is CF_3 . In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), R^7 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), R^7 is C_{1-4} haloalkyl. In certain embodiments, R^7 is CF_3 . In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), R^4 and R^7 are CF_3 or methyl. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), R^5 , R^6 , R^8 , and R^9 may be the same or different. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), R^5 , R^6 , R^8 , and R^9 are each independently hydrogen, halo, C_{1-2} alkyl, C_{1-2} haloalkyl, or C_{3-6} cycloalkyl. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), R^5 , R^6 , R^8 , and R^9 are hydrogen, methyl, or fluoro. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), R^5 and R^6 are C_{1-2} alkyl. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), R^5 and R^6 are methyl. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), R^8 and R^9 are C_{1-2} alkyl. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), R^8 and R^9 are methyl. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), two or more of R^4 , R^5 , and R^6 or R^7 , R^8 , and R^9 may join together to form one or more C_{3-6} cycloalkyl groups that are optionally substituted with halogen.

In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R^1 is a 5 to 6-membered heterocycle having 1 to 3 heteroatoms selected from N, O, and S, or a 5 to 6-membered heteroaryl having 1 to 3 heteroatoms selected from N, O, and S, wherein the 5 to 6-membered heterocycle or 5 to 6-membered heteroaryl is optionally substituted with 1 to 3 R^a

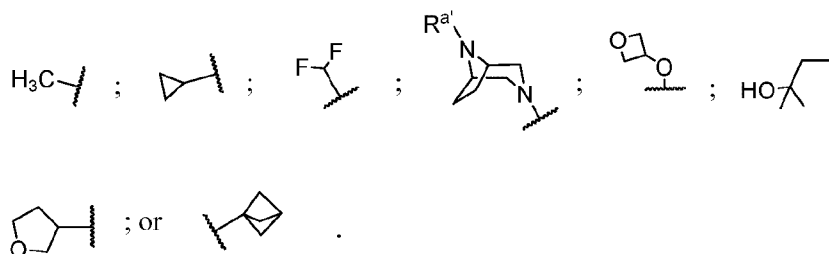
groups. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R¹ is a 5 to 6-membered heterocycle having 1 to 3 heteroatoms selected from N, O, and S and is optionally substituted with 1 to 3 R^a groups. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R¹ is:



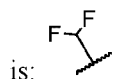
certain embodiments, R¹ is   or . In certain embodiments, R¹ is:



In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R^a is independently C₁₋₄alkyl, C₁₋₄alkyl with 1 to 2 groups selected from hydroxyl and C₁₋₄ alkoxy, C₁₋₄ haloalkyl, or a 4 to 8-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S optionally substituted with R^{a1}. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R^a is independently C₁₋₄alkyl, C₁₋₄alkyl with 1 to 2 groups selected from hydroxyl and C₁₋₄ alkoxy, C₁₋₄ haloalkyl, furanyl, oxetanyl, or 3,8-diazabicyclo[3.2.1]octanyl optionally substituted with R^{a1}. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R^a is independently C₁₋₄alkyl, C₁₋₄alkyl with 1 to 2 groups selected from hydroxyl and C₁₋₄ alkoxy, or C₁₋₄ haloalkyl. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R^a is:

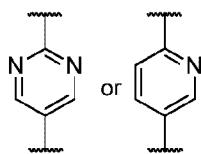


In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R^a is C_{1-4} haloalkyl. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R^a

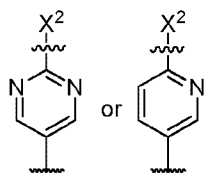


- 5 In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie) R^a may be substituted by R^{a1} . In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R^a is substituted with one R^{a1} group. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R^{a1} is C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or 4 to 8-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S. In certain
- 10 embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), the 4 to 8-membered heterocyclyl contains 1 to 2 nitrogen heteroatoms or 1 to 2 oxygen atoms.

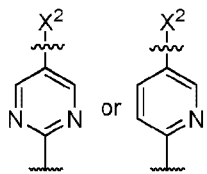
- In certain embodiments of a compound of Formula (I), (Ia), or (Ie), X^1 is a 6 -membered aryl or a 5 to 6-membered heteroaryl having 1 to 3 heteroatoms selected from N, O, and S, wherein each 6-membered aryl or 5 to 6-membered heteroaryl is optionally substituted with 1 to
- 15 4 R^b groups. In certain embodiments of a compound of Formula (I), (Ia), or (Ie), X^1 is pyrimidine or pyridine optionally substituted with 1 to 4 R^b groups. In certain embodiments of a compound of Formula (I), (Ia), or (Ie), X^1 is pyrimidine or pyridine. In certain embodiments of a compound of Formula (I), (Ia), or (Ie), X^1 is:



. In certain embodiments of a compound of Formula (I), (Ia), or (Ie),

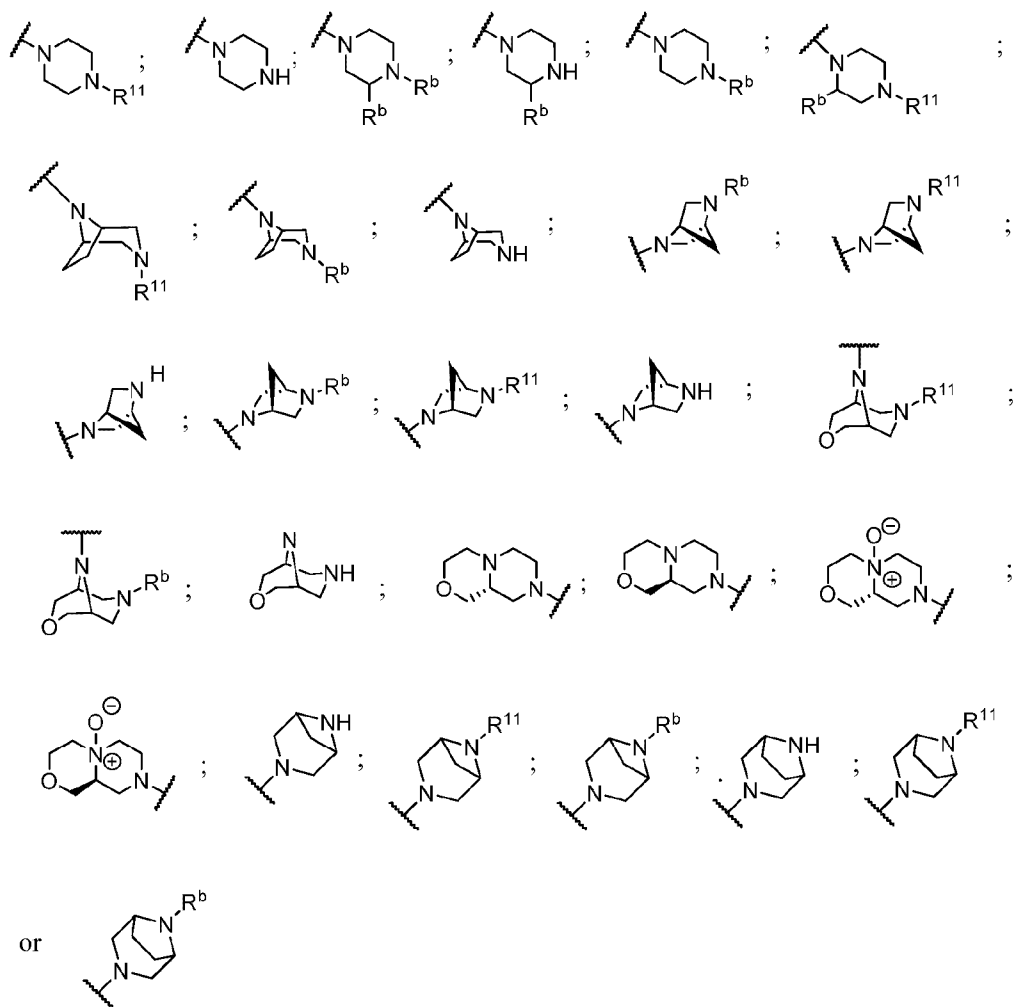


X^1 is . In certain embodiments of a compound of Formula (I), (Ia), or (Ie), X^1

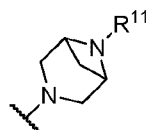


is .

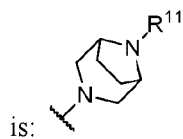
In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Id) or (Ie), X^2 is a 4 to
 5 10-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S and is
 optionally substituted with one R^{11} and optionally substituted with 1 to 5 R^b groups. In certain
 embodiments, X^2 may be substituted by R^{11} and R^b . In certain embodiments of a compound of
 Formula (I), (Ia), (Ib), (Id) or (Ie) X^2 is:



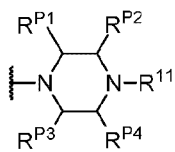
In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Id) or (Ie), X^2 is:



In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Id) or (Ie), X^2



5 In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Id) or (Ie) X^2 is



wherein:

a) R^{P1} , R^{P2} , R^{P3} , and R^{P4} are each hydrogen;

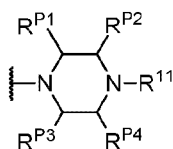
b) R^{P1} and R^{P3} are taken together to form a $-CH_2-$ or $-CH_2CH_2-$ group and R^{P2} and R^{P4} are each hydrogen;

c) R^{P2} and R^{P4} are taken together to form a $-CH_2-$ or $-CH_2CH_2-$ group and R^{P1} and R^{P3} are each hydrogen.

d) R^{P1} and R^{P4} are taken together to form a $-CH_2-$ group and R^{P2} and R^{P3} are each hydrogen; or

e) R^{P2} and R^{P3} are taken together to form a $-CH_2-$ group and R^{P1} and R^{P4} are each hydrogen.

10 In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Id) or (Ie) X^2 is



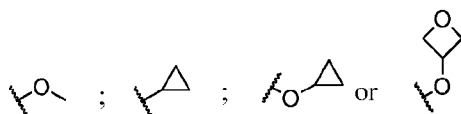
wherein:

R^{P1} and R^{P3} are taken together to form a $-CH_2-$ or $-CH_2CH_2-$ group and R^{P2} and R^{P4} are each hydrogen; or

R^{P2} and R^{P4} are taken together to form a $-CH_2-$ or $-CH_2CH_2-$ group and R^{P1} and R^{P3} are each hydrogen.

In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), X^2 is optionally substituted by R^{11} . In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R^{11} is 4 to 10-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R^{11} is a 4 to 6-membered heterocycle having one oxygen. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R^{11} is oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), R^{11} is oxetan-3-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl.

In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), or (Id), R^2 and R^3 may be the same or different. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), or (Id), R^2 and R^3 are each independently C_{1-4} alkyl, C_{3-6} cycloalkyl, or $O-R^{2A}$, wherein R^{2A} is C_{1-4} alkyl, C_{3-6} cycloalkyl, or a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S. In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), or (Id), R^2 and R^3 are each independently



In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), or (Id), R^2 and R^3 are each methoxy.

In certain embodiments of a compound of Formula (I), each R^{10} may be the same or different when n is greater than one. In some embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), or (Id), $n=0, 1$, or 2 . In certain embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), or (Id), each R^{10} is, halogen. In certain embodiments, each R^{10} is, chloro or fluoro.

In certain embodiments of a compound of Formula (Ia), (Ib), (Ic), or (Id), R^{10a} and R^{10b} may be the same or different. In certain embodiments of a compound of Formula (Ia), (Ib), (Ic), or (Id), R^{10a} and R^{10b} are each halogen. In certain of a compound of Formula (Ia), (Ib), (Ic), or (Id), R^{10a} and R^{10b} are each chloro or fluoro.

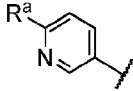
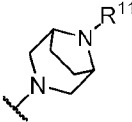
In certain embodiments of compound of Formula I, A is ethynyl. In certain embodiments of a compound of Formula I, A is a bond.

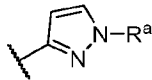
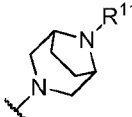
In certain embodiments, whenever present, each of X^1 and X^2 may be substituted by one or more R^b groups. In certain embodiments, each R^b is independently halogen, oxo, C_{1-4} alkyl, C_{1-4} alkyl with 1 to 2 groups selected from hydroxyl and C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} alkoxy, or $COO(R^e)$. In certain embodiments, each R^b is independently oxo or halo.

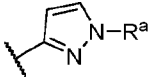
In certain embodiments of a compound of Formula I, each R^{12} is C_{1-2} alkyl, halo, $-OC_{1-2}$ alkyl or cyano. In certain embodiments of a compound of Formula I, R^{12} is fluoro, chloro, or methyl.

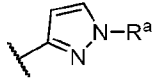
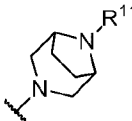
In certain embodiments of a compound of Formula (Ib) or (Ic), one of Z^1 and Z^2 is N and the other is CH. In certain embodiments of a compound of Formula (Ib) or (Ic), both of Z^1 and Z^2 are N.

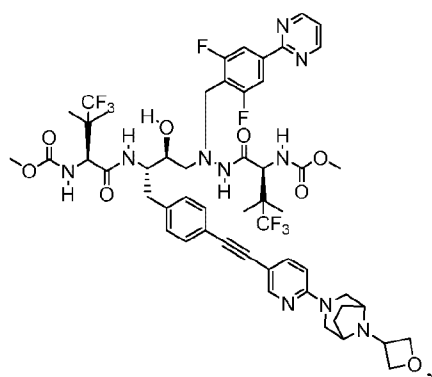
As disclosed above, any of the definitions for the variables provided (e.g. A, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{10a} , R^{10b} , Z^1 , Z^2 , X^1 , and X^2) may be combined and grouped with other variables, whether or not specifically recited together.

In certain embodiments of a compound of Formula (Ia), R^1 is  or ; R^a is C_{1-4} haloalkyl; X^1 is pyrimidine or pyridine, R^2 and R^3 are each methoxy, R^4 is CH_3 or CF_3 , R^7 is CH_3 or CF_3 , R^5 , R^6 , R^8 , and R^9 are each methyl, X^2 is: ; R^{10a} and R^{10b} are each halogen; and R^{11} is a 4 to 6-membered heterocycle having one oxygen.

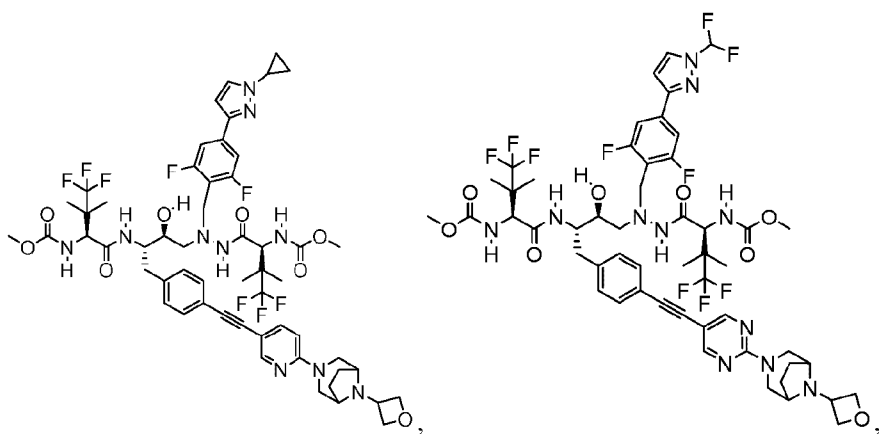
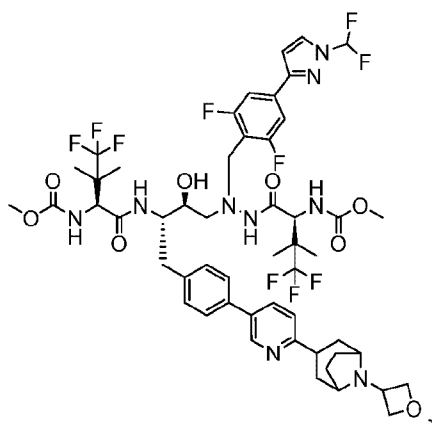
5 In certain embodiments of a compound of Formula (Ib), R^1 is ; R^a is C_{1-4} haloalkyl; m is 0, Z^1 and Z^2 are independently N or CH, R^2 and R^3 are each methoxy, R^4 is CH_3 or CF_3 , R^7 is CH_3 or CF_3 , R^5 , R^6 , R^8 , and R^9 are each methyl; X^2 is: ; R^{10a} and R^{10b} are each halogen; and R^{11} is a 4 to 6-membered heterocycle having one oxygen.

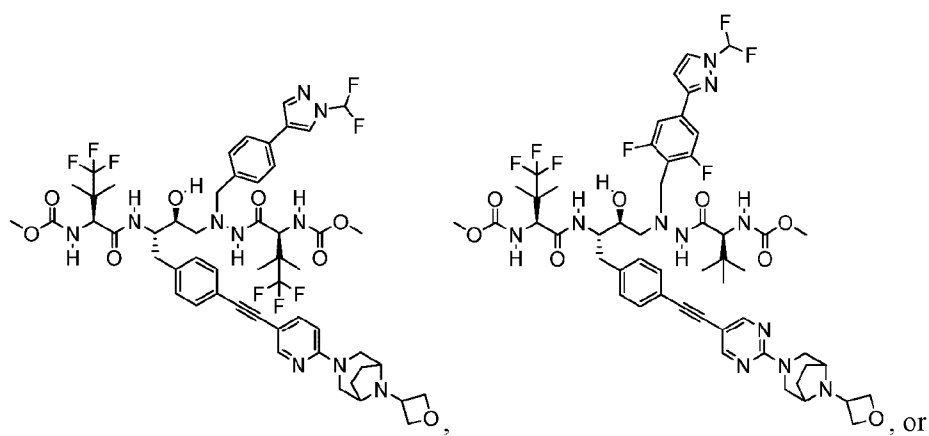
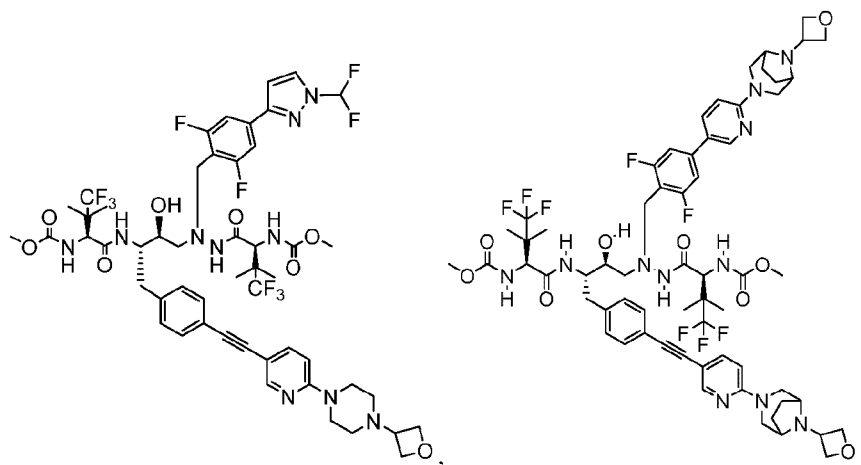
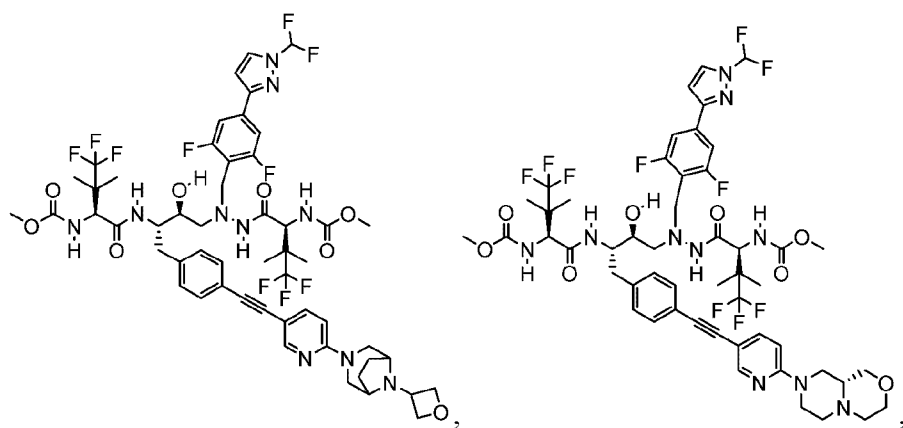
10 In certain embodiments of a compound of Formula (Ic), R^1 is ; R^a is C_{1-4} haloalkyl; Z^1 and Z^2 are independently N or CH, R^2 and R^3 are each methoxy, R^4 is CH_3 or CF_3 , R^7 is CH_3 or CF_3 , R^5 , R^6 , R^8 , and R^9 are each methyl; R^{10a} and R^{10b} are each halogen; and R^{11} is oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl.

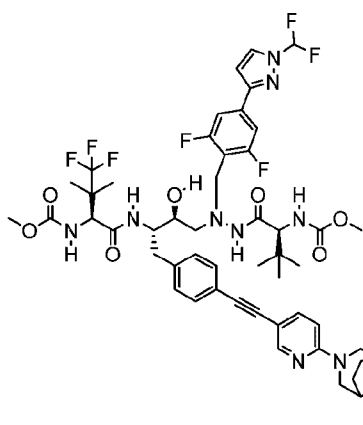
15 In certain embodiments of a compound of Formula (Id), R^1 is ; R^a is $-CH_2F$; X^1 is pyrimidine or pyridine, R^2 and R^3 are each methoxy, R^4 is CH_3 or CF_3 , R^7 is CH_3 or CF_3 , R^5 , R^6 , R^8 , and R^9 are each methyl, X^2 is: ; and R^{10a} and R^{10b} are each halogen, and R^{11} is oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl.



In certain embodiments, the compound is:



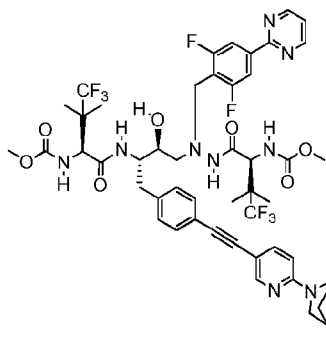




, or a pharmaceutically acceptable salt thereof.

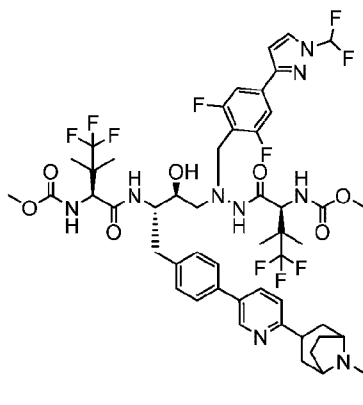
In certain embodiments, the compound is a compound of any of Examples 1-245, or a pharmaceutically acceptable salt thereof.

- 5 In certain embodiments, the compound is



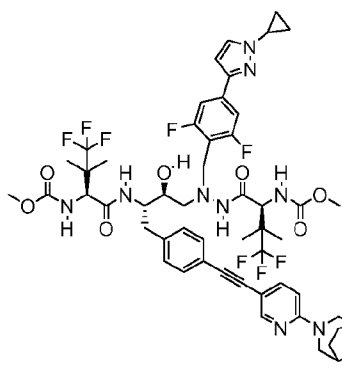
; or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



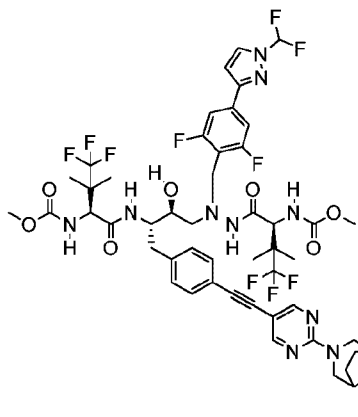
; or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



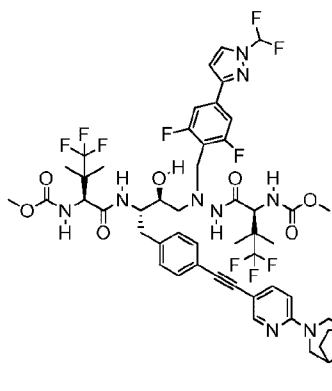
; or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



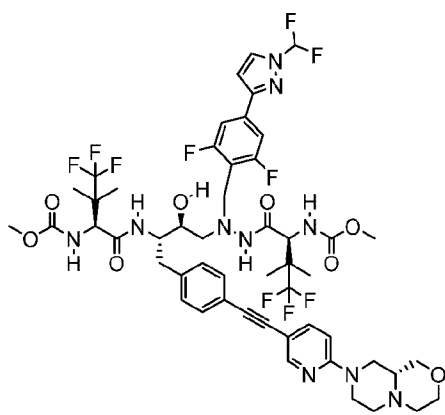
; or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



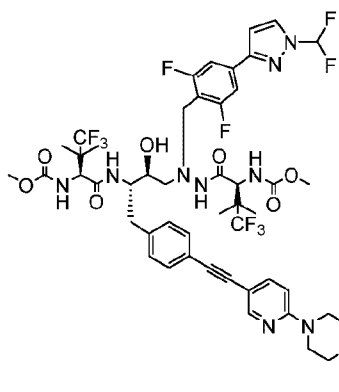
5 ; or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



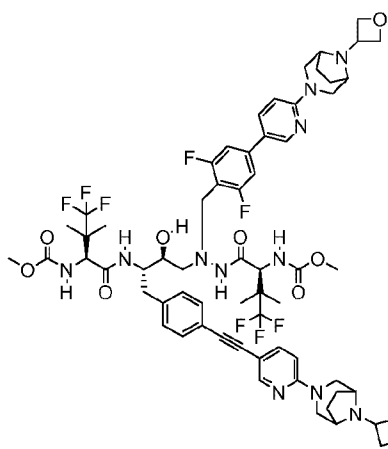
; or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



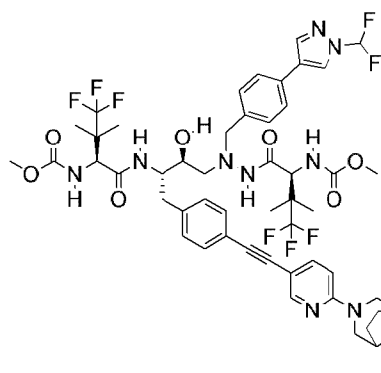
; or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



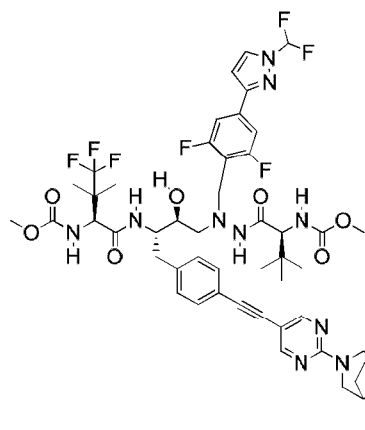
5 ; or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



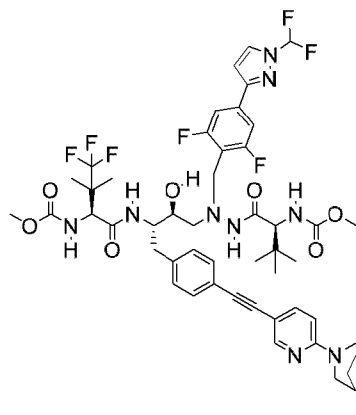
; or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



is; or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



5; or a pharmaceutically acceptable salt thereof.

METHODS OF TREATMENT

The pharmaceutical compositions of compounds of Formual (I) (including compounds of Formulae (Ia) - (Ie) may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, for example as described in those patents and patent applications cited herein, including rectal, buccal,

10

intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, as an inhalant, or via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer.

5 In one aspect, the compounds described herein may be administered orally. Oral administration may be via, for example, capsule or enteric coated tablets. In making the pharmaceutical compositions that include at least one compound of Formula (I), or a pharmaceutically acceptable salt, is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the
10 excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material (as above), which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin
15 capsules, sterile injectable solutions, and sterile packaged powders.

 Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc,
20 magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

 The compositions that include at least one compound of Formula (I), or a pharmaceutically acceptable salt, can be formulated so as to provide quick, sustained or delayed
25 release of the active ingredient after administration to the subject by employing procedures known in the art. Controlled-release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Examples of controlled release systems are given in U.S. Patent Nos. 3,845,770; 4,326,525; 4,902,514; and 5,616,345. Another formulation for use in the
30 methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g.,

U.S. Patent Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

The compositions may, in some embodiments, be formulated in a unit dosage form. The term “unit dosage forms” refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient (e.g., a tablet, capsule, ampoule). The compounds are generally administered in a pharmaceutically effective amount. In some embodiments, for oral administration, each dosage unit contains from about 10 mg to about 1000 mg of a compound described herein, for example from about 50 mg to about 500 mg, for example about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg. In other embodiments, for parenteral administration, each dosage unit contains from 0.1 to 700 mg of a compound a compound described herein. It will be understood, however, that the amount of the compound actually administered usually will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual subject, and the severity of the subject's symptoms.

In certain embodiments, dosage levels may be from 0.1 mg to 100 mg per kilogram of body weight per day, for example from about 1 mg to about 50 mg per kilogram, for example from about 5 mg to about 30 mg per kilogram. Such dosage levels may, in certain instances, be useful in the treatment of the above-indicated conditions. In other embodiments, dosage levels may be from about 10 mg to about 2000 mg per subject per day. The amount of active ingredient that may be combined with the vehicle to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms may contain from 1 mg to 1000 mg of an active ingredient.

The compounds disclosed herein, or a pharmaceutically acceptable salt thereof, may be administered to a subject in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one day, at least about one week, at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 6 months, or at least about 12 months or longer. In one variation, the compound is administered on a daily or intermittent schedule. In one variation, the compound is administered on a

monthly schedule. In one variation, the compound is administered every two months. In one variation, the compound is administered every three months. In one variation, the compound is administered every four months. In one variation, the compound is administered every five months. In one variation, the compound is administered every 6 months.

5 The dosage or dosing frequency of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, may be adjusted over the course of the treatment, based on the judgment of the administering physician. The compound may be administered to a subject (*e.g.*, a human) in an effective amount. In certain embodiments, the compound is administered once daily.

10 For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of Formula (I), or a pharmaceutically acceptable salt, thereof. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

15 The tablets or pills of the compounds described herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist
20 disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

25 In some embodiments, formulations suitable for parenteral administration (*e.g.*, intramuscular (IM) and subcutaneous (SC) administration) will include one or more excipients. Excipients should be compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof. Examples of suitable excipients are well known to the person skilled in the art of parenteral formulation and may be found *e.g.*, in Handbook of Pharmaceutical Excipients (eds. Rowe, Sheskey & Quinn), 6th edition 2009.

30 In some embodiments, the compounds described herein, or a pharmaceutically acceptable salt thereof, may be administered with a syringe. In some embodiments, the syringe is disposable. In some embodiments, the syringe is reusable. In some embodiments, the syringe

is pre-filled with a compound described herein, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds described herein, or a pharmaceutically acceptable salt thereof, may be administered with an auto-injector comprising a syringe. In some
5 embodiments, the syringe is disposable. In some embodiments, the syringe is reusable. In some
embodiments, the syringe is pre-filled with a compound described herein, or a pharmaceutically
acceptable salt thereof.

In certain embodiments, a method of treating or preventing a human immunodeficiency
virus (HIV) infection comprising administering a therapeutically effective amount of a
10 compound disclosed herein, or a pharmaceutically acceptable salt thereof, to a subject in need
thereof, is provided. In certain embodiments, a method of treating a human immunodeficiency
virus (HIV) infection comprising administering a therapeutically effective amount of a
compound disclosed herein, or a pharmaceutically acceptable salt thereof, to a subject in need
thereof, is provided. In certain embodiments, the method comprises administering a compound
15 disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one, two,
three, or four additional therapeutic agents. In certain embodiments, the subject is at risk of
contracting the HIV virus, such as a subject who has one or more risk factors known to be
associated with contracting the HIV virus. In certain embodiments, the subject may have not
previously received antiviral treatment (treatment naïve). In certain embodiments, the subject
20 may have previously received antiviral treatment (treatment experienced). In certain
embodiments, the subject may have previously received antiviral treatment and developed
resistance to the previously received antiviral treatment.

In certain embodiments, a method of treating or preventing a human immunodeficiency
virus (HIV) infection comprising administering a therapeutically effective amount of a
25 compound disclosed herein, or a pharmaceutically acceptable salt thereof, to a subject in need
thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two,
three, or four; or one or two; or one to three; or one to four) additional therapeutic agents
selected from the group consisting of combination drugs for HIV, other drugs for treating HIV,
HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse
30 transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase
inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV
maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-
based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific

antibodies and “antibody-like” therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT

5 protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL

10 protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof, is provided. In certain embodiments, the one or

15 more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120

20 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or any combinations thereof. In certain embodiments, the one or more additional therapeutic agent does not include a pharmacokinetic enhancer.

In certain embodiments, a method for inhibiting the replication of the HIV virus, treating AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human), comprising administering a

25 compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject is disclosed.

In certain embodiments, a compound of disclosed herein, or a pharmaceutically acceptable salt thereof for use in medical therapy of an HIV infection (*e.g.* HIV-1 or the replication of the HIV virus (*e.g.* HIV-1) or AIDS or delaying the onset of AIDS in a subject

30 (*e.g.*, a human)) is disclosed.

In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for treating an HIV infection or the replication of the HIV virus or AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human)

is disclosed. One embodiment relates to a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection or AIDS or for use in the therapeutic treatment or delaying the onset of AIDS.

5 In certain embodiments, the use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for an HIV infection in a subject (*e.g.*, a human) is disclosed. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection is disclosed.

10 In certain embodiments, in the methods of use, the administration is to a subject (*e.g.*, a human) in need of the treatment. In certain embodiments, in the methods of use, the administration is to a subject (*e.g.*, a human) who is at risk of developing AIDS.

The compounds disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy is provided. In one embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is for use in a method of treating an HIV infection or
15 the replication of the HIV virus or AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human).

The compounds disclosed herein, or a pharmaceutically acceptable salt thereof, for use in a method of treating or preventing HIV infection in a subject in need thereof is provided. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt
20 thereof, for use in a method of treating HIV infection in a subject in need thereof is provided. In certain embodiments, the subject in need thereof is a human who has been infected with HIV. In certain embodiments, the subject in need thereof is a human who has been infected with HIV but who has not developed AIDS. In certain embodiments, the subject in need thereof is a subject at risk for developing AIDS. In certain embodiments, the subject in need thereof is a human who
25 has been infected with HIV and who has developed AIDS.

In one embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more (*e.g.* one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents as described herein for use in a method of treating or preventing HIV infection in a subject in need thereof is provided. In one embodiment,
30 said additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse

transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and “antibody-like” therapeutic proteins, HIV p17 matrix

5 protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors,

10 integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9

15 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof. In certain embodiments, said additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide

20 inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or any combinations thereof.

In one embodiment, a compound disclosed herein, or a pharmaceutically acceptable

25 salt thereof, in combination with a first additional therapeutic agent selected from the group consisting of tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine, is provided for use in a method of treating or preventing HIV infection in a subject in need thereof. In a particular embodiment, a compound disclosed herein,

30 or a pharmaceutically acceptable salt thereof, in combination with a first additional therapeutic agent selected from the group consisting of tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir disoproxil hemifumarate, and a second additional therapeutic agent, wherein the

second additional therapeutic agent is emtricitabine, is provided for use in a method of treating or preventing HIV infection in a subject in need thereof.

In a particular embodiment, a compound disclosed herein or a pharmaceutically acceptable salt thereof, are provided for use to prevent HIV infection from taking hold if the individual is exposed to the virus and/or to keep the virus from establishing a permanent infection and/or to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectable levels in the blood, for example for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Accordingly, in certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) are provided. For example, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a pharmaceutical composition comprising a therapeutically effective amount of the compound disclosed herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with safer sex practices. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration to an individual at risk of acquiring HIV. Examples of individuals at high risk for acquiring HIV include, without limitation, an individual who is at risk of sexual transmission of HIV.

In certain embodiments, the reduction in risk of acquiring HIV is at least about 40%, 50%, 60%, 70%, 80%, 90%, or 95%. In certain embodiments, the reduction in risk of acquiring HIV is at least about 75%. In certain embodiments, the reduction in risk of acquiring HIV is about 80%, 85%, or 90%.

In another embodiment, the use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of an HIV infection in a human being having or at risk of having the infection is disclosed.

Also disclosed herein is a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the therapeutic treatment or delaying the onset of AIDS.

Also disclosed herein is a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection.

5 In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof can be used as a research tool (e.g. to study the inhibition of HIV reverse transcriptase in a subject or *in vitro*).

 Kits that include a compound of Formula (I), or a pharmaceutically acceptable salt, thereof, and suitable packaging are provided. In one embodiment, a kit further includes
10 instructions for use. In one aspect, a kit includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and instructions for use of the compounds in the treatment of the diseases or conditions described herein.

 Articles of manufacture that include a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a suitable container are provided. The container may be a vial, jar,
15 ampoule, preloaded syringe, and intravenous bag.

Administration of HIV Combination Therapy

 In certain embodiments, a compound disclosed herein is administered with one or more additional therapeutic agents. Co-administration of a compound disclosed herein with one or more additional therapeutic agents generally refers to simultaneous or sequential administration
20 of a compound disclosed herein and one or more additional therapeutic agents, such that therapeutically effective amounts of the compound disclosed herein and the one or more additional therapeutic agents are both present in the body of the patient. When administered sequentially, the combination may be administered in two or more administrations.

 Co-administration includes administration of unit dosages of the compounds disclosed
25 herein before or after administration of unit dosages of one or more additional therapeutic agents. For example, the compound disclosed herein may be administered within seconds, minutes, or hours of the administration of the one or more additional therapeutic agents. In some embodiments, a unit dose of a compound disclosed herein is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents.
30 Alternatively, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound disclosed herein within seconds or minutes. In other embodiments, a unit dose of a compound disclosed herein is administered first,

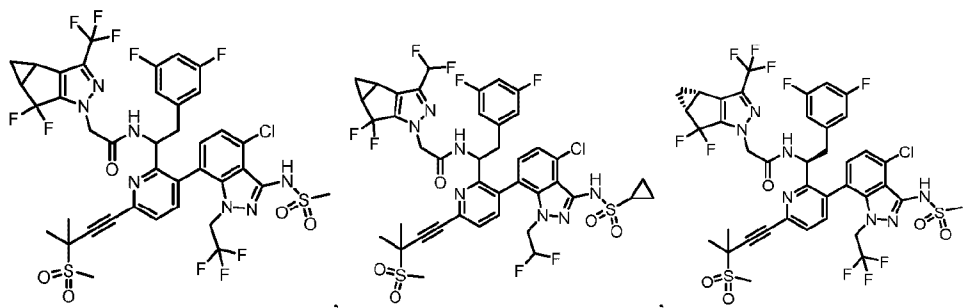
followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In yet other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound disclosed herein.

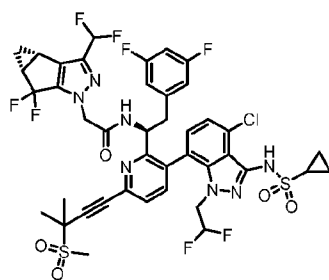
- 5 In certain embodiments, a compound disclosed herein is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a patient, for example as a solid dosage form for oral administration.

In certain embodiments, a compound of Formula (I) is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HIV. In certain
10 embodiments, the tablet can contain another active ingredient for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

15 In some embodiments, a compound of Formula (I) is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can contain another active ingredient for treating HIV, such as compounds that target the HIV capsid, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse
20 transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

In some embodiments, the compounds that target the HIV capsid are selected from the group consisting of:





and , or a pharmaceutically acceptable salt thereof.

In certain embodiments, such tablets are suitable for once daily dosing.

HIV Combination Therapy

5 In the above embodiments, the additional therapeutic agent may be an anti-HIV agent. HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and “antibody-like” therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT

15 protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL

20 protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, HIV vaccines, and combinations thereof.

25 In some embodiments, the additional therapeutic agent is selected from immunomodulators, immunotherapeutic agents, antibody-drug conjugates, gene modifiers, gene editors (such as CRISPR/Cas9, zinc finger nucleases, homing nucleases, synthetic nucleases,

TALENs), and cell therapies such as chimeric antigen receptor T-cell, CAR-T (e.g., YESCARTA® (axicabtagene ciloleucel)), and engineered T cell receptors, TCR-T.

In some embodiments, the additional therapeutic agent is selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV non-catalytic site (or
 5 allosteric) integrase inhibitors, HIV entry (fusion) inhibitors, HIV maturation inhibitors, latency reversing agents, capsid inhibitors, immune-based therapies, PI3K inhibitors, HIV antibodies, and bispecific antibodies, and “antibody-like” therapeutic proteins, and combinations thereof.

HIV Combination Drugs

10 Examples of combination drugs include ATRIPLA® (efavirenz, tenofovir disoproxil fumarate, and emtricitabine); COMPLERA® (EVIPLERA®; rilpivirine, tenofovir disoproxil fumarate, and emtricitabine); STRIBILD® (elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine); TRUVADA® (tenofovir disoproxil fumarate and emtricitabine; TDF+FTC); DESCOVY® (tenofovir alafenamide and emtricitabine); ODEFSEY® (tenofovir
 15 alafenamide, emtricitabine, and rilpivirine); GENVOYA® (tenofovir alafenamide, emtricitabine, cobicistat, and elvitegravir); darunavir, tenofovir alafenamide hemifumarate, emtricitabine, and cobicistat; efavirenz, lamivudine, and tenofovir disoproxil fumarate; lamivudine and tenofovir disoproxil fumarate; tenofovir and lamivudine; tenofovir alafenamide and emtricitabine; tenofovir alafenamide hemifumarate and emtricitabine; tenofovir alafenamide
 20 hemifumarate, emtricitabine, and rilpivirine; tenofovir alafenamide hemifumarate, emtricitabine, cobicistat, and elvitegravir; COMBIVIR® (zidovudine and lamivudine; AZT+3TC); EPZICOM® (LIVEXA®; abacavir sulfate and lamivudine; ABC+3TC); KALETRA® (ALUVIA®; lopinavir and ritonavir); TRIUMEQ® (dolutegravir, abacavir, and lamivudine); TRIZIVIR® (abacavir sulfate, zidovudine, and lamivudine; ABC+AZT+3TC); atazanavir and cobicistat; atazanavir
 25 sulfate and cobicistat; atazanavir sulfate and ritonavir; darunavir and cobicistat; dolutegravir and rilpivirine; dolutegravir and rilpivirine hydrochloride; dolutegravir, abacavir sulfate, and lamivudine; lamivudine, nevirapine, and zidovudine; raltegravir and lamivudine; doravirine, lamivudine, and tenofovir disoproxil fumarate; doravirine, lamivudine, and tenofovir disoproxil; dolutegravir + lamivudine, lamivudine + abacavir + zidovudine, lamivudine + abacavir,
 30 lamivudine + tenofovir disoproxil fumarate, lamivudine + zidovudine + nevirapine, lopinavir + ritonavir, lopinavir + ritonavir + abacavir + lamivudine, lopinavir + ritonavir + zidovudine + lamivudine, tenofovir + lamivudine, and tenofovir disoproxil fumarate + emtricitabine +

rilpivirine hydrochloride, lopinavir, ritonavir, zidovudine and lamivudine; Vacc-4x and romidepsin; and APH-0812.

Other HIV Drugs

Examples of other drugs for treating HIV include acemannan, alisporivir, BanLec, 5 deferiprone, Gamimmune, metenkefalin, naltrexone, Prolastin, REP 9, RPI-MN, VSSP, H1viral, SB-728-T, 1,5-dicaffeoylquinic acid, rHIV7-sh1-TAR-CCR5RZ, AAV-eCD4-Ig gene therapy, MazF gene therapy, BlockAide, ABX-464, AG-1105, APH-0812, BIT-225, CYT-107, HGTV-43, HPH-116, HS-10234, IMO-3100, IND-02, MK-1376, MK-8507, MK-8591, NOV-205, PA-1050040 (PA-040), PGN-007, SCY-635, SB-9200, SCB-719, TR-452, TEV-90110, TEV-10 90112, TEV-90111, TEV-90113, RN-18, Immuglo, and VIR-576.

HIV Protease Inhibitors

Examples of HIV protease inhibitors include amprenavir, atazanavir, brexanavir, darunavir, fosamprenavir, fosamprenavir calcium, indinavir, indinavir sulfate, lopinavir, nelfinavir, nelfinavir mesylate, ritonavir, saquinavir, saquinavir mesylate, tipranavir, DG-17, 15 TMB-657 (PPL-100), T-169, BL-008, and TMC-310911.

HIV Reverse Transcriptase Inhibitors

Examples of HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase include dapivirine, delavirdine, delavirdine mesylate, doravirine, efavirenz, etravirine, lentinan, nevirapine, rilpivirine, AIC-292, KM-023, and VM-1500.

20 In some embodiments, examples of HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase include dapivirine, delavirdine, delavirdine mesylate, doravirine, efavirenz, etravirine, lentinan, nevirapine, rilpivirine, AIC-292, KM-023, PC-1005, and VM-1500.

Examples of HIV nucleoside or nucleotide inhibitors of reverse transcriptase include adefovir, adefovir dipivoxil, azvudine, emtricitabine, tenofovir, tenofovir alafenamide, tenofovir 25 alafenamide fumarate, tenofovir alafenamide hemifumarate, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, VIDEX[®] and VIDEX EC[®] (didanosine, ddl), abacavir, abacavir sulfate, alovudine, apricitabine, censavudine, didanosine, elvucitabine, festinavir, fosaltuvudine tidoxil, CMX-157, dapivirine, doravirine, etravirine, OCR-5753, tenofovir disoproxil orotate, fozivudine tidoxil, lamivudine, phosphazid, stavudine, zalcitabine, 30 zidovudine, GS-9131, GS-9148, and KP-1461.

HIV Integrase Inhibitors

Examples of HIV integrase inhibitors include elvitegravir, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, raltegravir, dolutegravir, JTK-351, bicitegravir, AVX-15567, cabotegravir (long-acting injectable), diketo quinolin-4-1 derivatives, integrase-LEDGF inhibitor, ledgins, M-522, M-532, NSC-310217, NSC-371056, NSC-48240, NSC-642710, NSC-699171, NSC-699172, NSC-699173, NSC-699174, stilbenedisulfonic acid, T-169 and cabotegravir.

Examples of HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) include CX-05045, CX-05168, and CX-14442.

HIV Entry Inhibitors

Examples of HIV entry (fusion) inhibitors include cenicriviroc, CCR5 inhibitors, gp41 inhibitors, CD4 attachment inhibitors, gp120 inhibitors, and CXCR4 inhibitors.

Examples of CCR5 inhibitors include aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, adaptavir (RAP-101), nifeviroc (TD-0232), anti-GP120/CD4 or CCR5 bispecific antibodies, B-07, MB-66, polypeptide C25P, TD-0680, and vMIP (Haimipu).

Examples of gp41 inhibitors include albuvirtide, enfuvirtide, BMS-986197, enfuvirtide biobetter, enfuvirtide biosimilar, HIV-1 fusion inhibitors (P26-Bapc), ITV-1, ITV-2, ITV-3, ITV-4, PIE-12 trimer and sifuvirtide.

Examples of CD4 attachment inhibitors include ibalizumab and CADA analogs

Examples of gp120 inhibitors include Radha-108 (receptol) 3B3-PE38, BanLec, bentonite-based nanomedicine, fostemsavir tromethamine, IQP-0831, and BMS-663068

Examples of CXCR4 inhibitors include plerixafor, ALT-1188, N15 peptide, and vMIP (Haimipu).

HIV Maturation Inhibitors

Examples of HIV maturation inhibitors include BMS-955176 and GSK-2838232.

Latency Reversing Agents

Examples of latency reversing agents include histone deacetylase (HDAC) inhibitors, proteasome inhibitors such as velcade, protein kinase C (PKC) activators, BET-bromodomain 4 (BRD4) inhibitors, ionomycin, PMA, SAHA (suberanilohydroxamic acid, or suberoyl, anilide, and hydroxamic acid), IL-15, JQ1, disulfiram, amphotericin B, and ubiquitin inhibitors such as largazole analogs, and GSK-343.

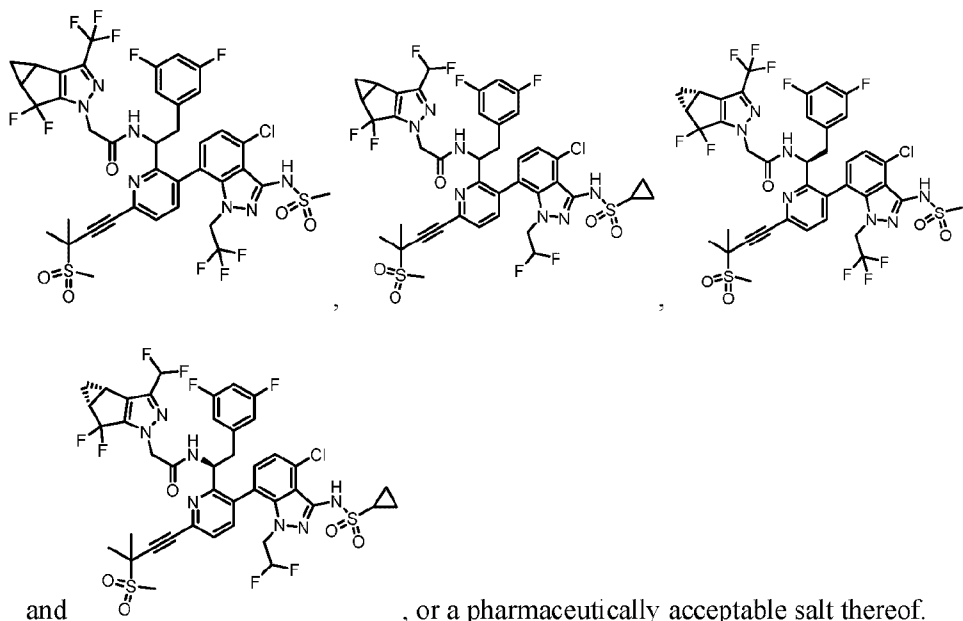
Examples of HDAC inhibitors include romidepsin, vorinostat, and panobinostat.

Examples of PKC activators include indolactam, prostratin, ingenol B, and DAG-lactones.

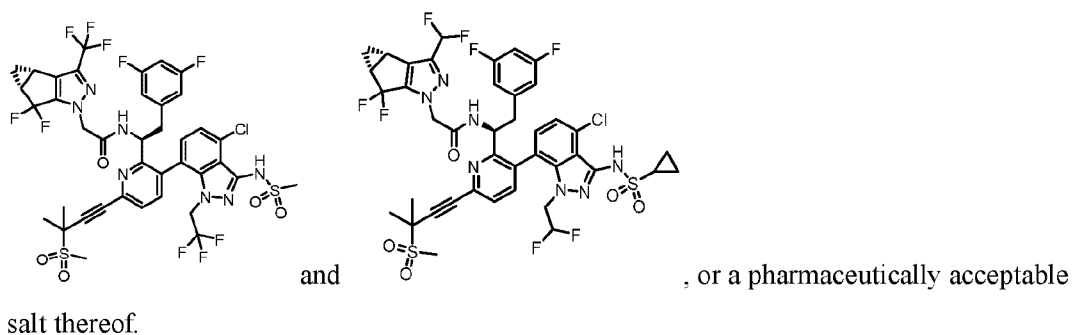
10 *Capsid Inhibitors*

Examples of capsid inhibitors include capsid polymerization inhibitors or capsid disrupting compounds, HIV nucleocapsid p7 (NCp7) inhibitors such as azodicarbonamide, HIV p24 capsid protein inhibitors, AVI-621, AVI-101, AVI-201, AVI-301, and AVI-CAN1-15 series;

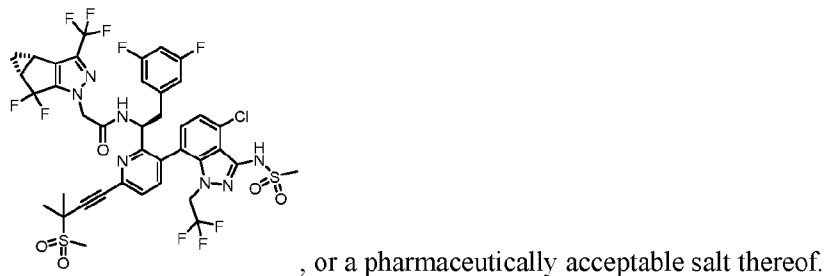
15 In some embodiments, examples of capsid inhibitors include:



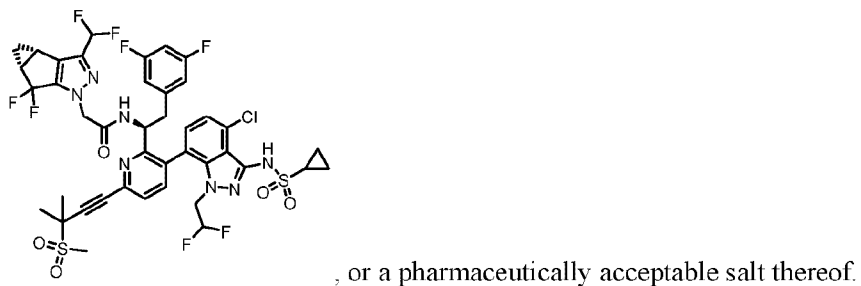
In some embodiments, the capsid inhibitor is selected from:



In some embodiments, the capsid inhibitor is:



5 In some embodiments, the capsid inhibitor is:



Immune-based Therapies

Examples of immune-based therapies include toll-like receptors modulators such as tlr1, tlr2, tlr3, tlr4, tlr5, tlr6, tlr7, tlr8, tlr9, tlr10, tlr11, tlr12, and tlr13; programmed cell death protein 1 (Pd-1) modulators; programmed death-ligand 1 (Pd-L1) modulators; IL-15 agonists; DermaVir; interleukin-7; plaquenil (hydroxychloroquine); proleukin (aldesleukin, IL-2); interferon alfa; interferon alfa-2b; interferon alfa-n3; pegylated interferon alfa; interferon gamma; hydroxyurea; mycophenolate mofetil (MPA) and its ester derivative mycophenolate mofetil (MMF); ribavirin; rintatolimod, polymer polyethyleneimine (PEI); gepon; rintatolimod; IL-12; WF-10; VGV-1; MOR-22; BMS-936559; CYT-107, interleukin-15/Fc fusion protein, normferon, peginterferon alfa-2a, peginterferon alfa-2b, recombinant interleukin-15, RPI-MN, GS-9620, and IR-103.

In some embodiments, examples of immune-based therapies include toll-like receptors modulators such as tlr1, tlr2, tlr3, tlr4, tlr5, tlr6, tlr7, tlr8, tlr9, tlr10, tlr11, tlr12, and tlr13; programmed cell death protein 1 (Pd-1) modulators; programmed death-ligand 1 (Pd-L1) modulators; IL-15 agonists; DermaVir; interleukin-7; plaquenil (hydroxychloroquine); proleukin (aldesleukin, IL-2); interferon alfa; interferon alfa-2b; interferon alfa-n3; pegylated interferon alfa; interferon gamma; hydroxyurea; mycophenolate mofetil (MPA) and its ester derivative mycophenolate mofetil (MMF); ribavirin; rintatolimod, polymer polyethyleneimine (PEI); gepon; rintatolimod; IL-12; WF-10; VGV-1; MOR-22; BMS-936559; CYT-107, interleukin-15/Fc fusion protein, normferon, peginterferon alfa-2a, peginterferon alfa-2b, recombinant
 5 interleukin-15, RPI-MN, GS-9620, STING modulators, RIG-I modulators, NOD2 modulators,
 10 and IR-103.

Phosphatidylinositol 3-kinase (PI3K) Inhibitors

Examples of PI3K inhibitors include idelalisib, alpelisib, buparlisib, CAI orotate, copanlisib, duvelisib, gedatolisib, neratinib, panulisib, perifosine, pictilisib, pilaralisib,
 15 puquitinib mesylate, rigosertib, rigosertib sodium, sonolisib, taselisib, AMG-319, AZD-8186, BAY-1082439, CLR-1401, CLR-457, CUDC-907, DS-7423, EN-3342, GSK-2126458, GSK-2269577, GSK-2636771, INCB-040093, LY-3023414, MLN-1117, PQR-309, RG-7666, RP-6530, RV-1729, SAR-245409, SAR-260301, SF-1126, TGR-1202, UCB-5857, VS-5584, XL-765, and ZSTK-474.

20 *alpha-4/beta-7 antagonists*

Examples of Integrin alpha-4/beta-7 antagonists include PTG-100, TRK-170, abrilumab, etrolizumab, carotegrast methyl, and vedolizumab.

HIV Antibodies, Bispecific Antibodies, and "Antibody-like" Therapeutic Proteins

Examples of HIV antibodies, bispecific antibodies, and "antibody-like" therapeutic
 25 proteins include DARTs[®], DUOBODIES[®], BITES[®], XmAbs[®], TandAbs[®], Fab derivatives, bnABs (broadly neutralizing HIV-1 antibodies), BMS-936559, TMB-360, and those targeting HIV gp120 or gp41, antibody-Recruiting Molecules targeting HIV, anti-CD63 monoclonal antibodies, anti-GB virus C antibodies, anti-GP120/CD4, CCR5 bispecific antibodies, anti-nef single domain antibodies, anti-Rev antibody, camelid derived anti-CD18 antibodies, camelid-
 30 derived anti-ICAM-1 antibodies, DCVax-001, gp140 targeted antibodies, gp41-based HIV therapeutic antibodies, human recombinant mAbs (PGT-121), ibalizumab, Immuglo, MB-66

Examples of those targeting HIV in such a manner include bavituximab, UB-421, C2F5, C2G12, C4E10, C2F5+C2G12+C4E10, 3-BNC-117, PGT145, PGT121, MDX010 (ipilimumab), VRC01, A32, 7B2, 10E8, VRC-07-523, VRC-HIVMAB080-00-AB, MGD-014 and VRC07.

In some embodiments, examples of those targeting HIV in such a manner include
 5 bavituximab, UB-421, C2F5, 2G12, C4E10, C2F5+C2G12+C4E10, 8ANC195, 3BNC117, 3BNC60, 10-1074, PGT145, PGT121, PGT-151, PGT-133, MDX010 (ipilimumab), DH511, N6, VRC01 PGDM1400, A32, 7B2, 10E8, 10E8v4, CAP256-VRC26.25, DRVIA7, VRC-07-523, VRC-HIVMAB080-00-AB, VRC-HIVMAB060-00-AB, MGD-014 and VRC07. Example of HIV bispecific antibodies include MGD014.

10 *Pharmacokinetic Enhancers*

Examples of pharmacokinetic enhancers include cobicistat and ritonavir.

Additional Therapeutic Agents

Examples of additional therapeutic agents include the compounds disclosed in WO 2004/096286 (Gilead Sciences), WO 2006/015261 (Gilead Sciences), WO 2006/110157 (Gilead
 15 Sciences), WO 2012/003497 (Gilead Sciences), WO 2012/003498 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO 2013/006738 (Gilead Sciences), WO 2013/159064 (Gilead Sciences), WO 2014/100323 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), US 2014/0221378 (Japan Tobacco), US 2014/0221380 (Japan Tobacco), WO 2009/062285 (Boehringer Ingelheim), WO 2010/130034 (Boehringer Ingelheim), WO 2013/006792 (Pharma
 20 Resources), US 20140221356 (Gilead Sciences), US 20100143301 (Gilead Sciences) and WO 2013/091096 (Boehringer Ingelheim).

HIV Vaccines

Examples of HIV vaccines include peptide vaccines, recombinant subunit protein vaccines, live vector vaccines, DNA vaccines, CD4-derived peptide vaccines, vaccine
 25 combinations, rgp120 (AIDSVAX), ALVAC HIV (vCP1521)/AIDSVAX B/E (gp120) (RV144), monomeric gp120 HIV-1 subtype C vaccine, Remune, ITV-1, Contre Vir, Ad5-ENVA-48, DCVax-001 (CDX-2401), Vacc-4x, Vacc-C5, VAC-3S, multiclade DNA recombinant adenovirus-5 (rAd5), Pennvax-G, Pennvax-GP, HIV-TriMix-mRNA vaccine, HIV-LAMP-vax, Ad35, Ad35-GRIN, NAcGM3/VSSP ISA-51, poly-ICLC adjuvanted vaccines, TatImmune,
 30 GTU-multiHIV (FIT-06), gp140[delta]V2.TV1+MF-59, rVSVIN HIV-1 gag vaccine, SeV-Gag vaccine, AT-20, DNK-4, ad35-Grin/ENV, TBC-M4, HIVAX, HIVAX-2, NYVAC-HIV-PT1, NYVAC-HIV-PT4, DNA-HIV-PT123, rAAV1-PG9DP, GOVX-B11, GOVX-B21, TVI-HIV-1,

- Ad-4 (Ad4-env Clade C+Ad4-mGag), EN41-UGR7C, EN41-FPA2, PreVaxTat, AE-H, MYM-V101, CombiHIVvac, ADVAX, MYM-V201, MVA-CMDR, DNA-Ad5 gag/pol/nef/nev (HVTN505), MVATG-17401, ETV-01, CDX-1401, rcAD26.MOS1.HIV-Env, Ad26.Mod.HIV vaccine, AGS-004, AVX-101, AVX-201, PEP-6409, SAV-001, ThV-01, TL-01, TUTI-16,
- 5 VGX-3300, IHV-001, and virus-like particle vaccines such as pseudovirion vaccine, CombiVICHvac, LFn-p24 B/C fusion vaccine, GTU-based DNA vaccine, HIV gag/pol/nef/env DNA vaccine, anti-TAT HIV vaccine, conjugate polypeptides vaccine, dendritic-cell vaccines, gag-based DNA vaccine, GI-2010, gp41 HIV-1 vaccine, HIV vaccine (PIKA adjuvant), I i-key/MHC class II epitope hybrid peptide vaccines, ITV-2, ITV-3, ITV-4, LIPO-5, multiclade
- 10 Env vaccine, MVA vaccine, Pennvax-GP, pp71-deficient HCMV vector HIV gag vaccine, recombinant peptide vaccine (HIV infection), NCI, rgp160 HIV vaccine, RNActive HIV vaccine, SCB-703, Tat Oyi vaccine, TBC-M4, therapeutic HIV vaccine, UBI HIV gp120, Vacc-4x + romidepsin, variant gp120 polypeptide vaccine, rAd5 gag-pol env A/B/C vaccine.

- In some embodiments, examples of HIV vaccines include peptide vaccines, recombinant
- 15 subunit protein vaccines, live vector vaccines, DNA vaccines, CD4-derived peptide vaccines, vaccine combinations, rgp120 (AIDSVAX), ALVAC HIV (vCP1521)/AIDSVAX B/E (gp120) (RV144), monomeric gp120 HIV-1 subtype C vaccine, Remune, ITV-1, Contre Vir, Ad5-ENVA-48, DCVax-001 (CDX-2401), Vacc-4x, Vacc-C5, VAC-3S, multiclade DNA recombinant adenovirus-5 (rAd5), Pennvax-G, Pennvax-GP, HIV-TriMix-mRNA vaccine, HIV-
- 20 LAMP-vax, Ad35, Ad35-GRIN, NAcGM3/VSSP ISA-51, poly-ICLC adjuvanted vaccines, TatImmune, GTU-multiHIV (FIT-06), gp140[delta]V2.TV1+MF-59, rVSVIN HIV-1 gag vaccine, SeV-Gag vaccine, AT-20, DNK-4, ad35-Grin/ENV, TBC-M4, HIVAX, HIVAX-2, NYVAC-HIV-PT1, NYVAC-HIV-PT4, DNA-HIV-PT123, rAAV1-PG9DP, GOVX-B11, GOVX-B21, TVI-HIV-1, Ad-4 (Ad4-env Clade C+Ad4-mGag), EN41-UGR7C, EN41-FPA2,
- 25 PreVaxTat, AE-H, MYM-V101, CombiHIVvac, ADVAX, MYM-V201, MVA-CMDR, DNA-Ad5 gag/pol/nef/nev (HVTN505), MVATG-17401, ETV-01, CDX-1401, rcAD26.MOS1.HIV-Env, Ad26.Mod.HIV vaccine, AGS-004, AVX-101, AVX-201, PEP-6409, SAV-001, ThV-01, TL-01, TUTI-16, VGX-3300, IHV-001, and virus-like particle vaccines such as pseudovirion vaccine, CombiVICHvac, LFn-p24 B/C fusion vaccine, GTU-based DNA vaccine, HIV
- 30 gag/pol/nef/env DNA vaccine, anti-TAT HIV vaccine, conjugate polypeptides vaccine, dendritic-cell vaccines, gag-based DNA vaccine, GI-2010, gp41 HIV-1 vaccine, HIV vaccine (PIKA adjuvant), I i-key/MHC class II epitope hybrid peptide vaccines, ITV-2, ITV-3, ITV-4, LIPO-5, multiclade Env vaccine, MVA vaccine, Pennvax-GP, pp71-deficient HCMV vector

HIV gag vaccine, recombinant peptide vaccine (HIV infection), NCI, rgp160 HIV vaccine, RNActive HIV vaccine, SCB-703, Tat Oyi vaccine, TBC-M4, therapeutic HIV vaccine, UBI HIV gp120, Vacc-4x + romidepsin, variant gp120 polypeptide vaccine, rAd5 gag-pol env A/B/C vaccine, DNA.HTI and MVA.HTI.

5 *HIV Combination Therapy*

In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four or more additional therapeutic agents selected from ATRIPLA[®] (efavirenz, tenofovir disoproxil fumarate, and emtricitabine); COMPLERA[®] (EVIPLERA[®]; rilpivirine, tenofovir disoproxil fumarate, and emtricitabine);

10 STRIBILD[®] (elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine); TRUVADA[®] (tenofovir disoproxil fumarate and emtricitabine; TDF +FTC); DESCOVY[®] (tenofovir alafenamide and emtricitabine); ODEFSEY[®] (tenofovir alafenamide, emtricitabine, and rilpivirine); GENVOYA[®] (tenofovir alafenamide, emtricitabine, cobicistat, and elvitegravir); adefovir; adefovir dipivoxil; cobicistat; emtricitabine; tenofovir; tenofovir

15 disoproxil; tenofovir disoproxil fumarate; tenofovir alafenamide; tenofovir alafenamide hemifumarate; TRIUMEQ[®] (dolutegravir, abacavir, and lamivudine); dolutegravir, abacavir sulfate, and lamivudine; raltegravir; raltegravir and lamivudine; maraviroc; enfuvirtide; ALUVIA[®] (KALETRA[®]; lopinavir and ritonavir); COMBIVIR[®] (zidovudine and lamivudine; AZT+3TC); EPZICOM[®] (LIVEXA[®]; abacavir sulfate and lamivudine; ABC+3TC); TRIZIVIR[®]

20 (abacavir sulfate, zidovudine, and lamivudine; ABC+AZT+3TC); rilpivirine; rilpivirine hydrochloride; atazanavir sulfate and cobicistat; atazanavir and cobicistat; darunavir and cobicistat; atazanavir; atazanavir sulfate; dolutegravir; elvitegravir; ritonavir; atazanavir sulfate and ritonavir; darunavir; lamivudine; prolastin; fosamprenavir; fosamprenavir calcium efavirenz; etravirine; nelfinavir; nelfinavir mesylate; interferon; didanosine; stavudine;

25 indinavir; indinavir sulfate; tenofovir and lamivudine; zidovudine; nevirapine; saquinavir; saquinavir mesylate; aldesleukin; zalcitabine; tipranavir; amprenavir; delavirdine; delavirdine mesylate; Radha-108 (receptol); lamivudine and tenofovir disoproxil fumarate; efavirenz, lamivudine, and tenofovir disoproxil fumarate; phosphazid; lamivudine, nevirapine, and zidovudine; abacavir; and abacavir sulfate.

30 It will be appreciated by one of skill in the art that the additional therapeutic agents listed above may be included in more than one of the classes listed above. The particular classes are not intended to limit the functionality of those compounds listed in those classes.

In a specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is
5 combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer. In certain embodiments, a compound disclosed herein, or a
10 pharmaceutically acceptable salt thereof, is combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer. In another embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with abacavir sulfate, bictegravir, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir
15 alafenamide, or tenofovir alafenamide hemifumarate.

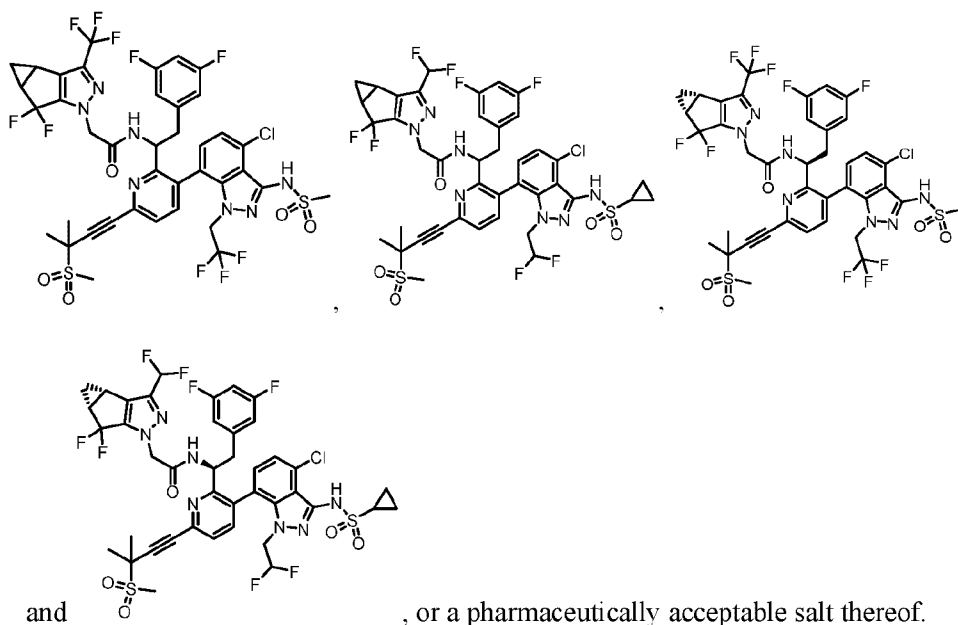
In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with tenofovir, tenofovir disoproxil, tenofovir disoproxil
20 fumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of abacavir sulfate, bictegravir, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a
25 second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

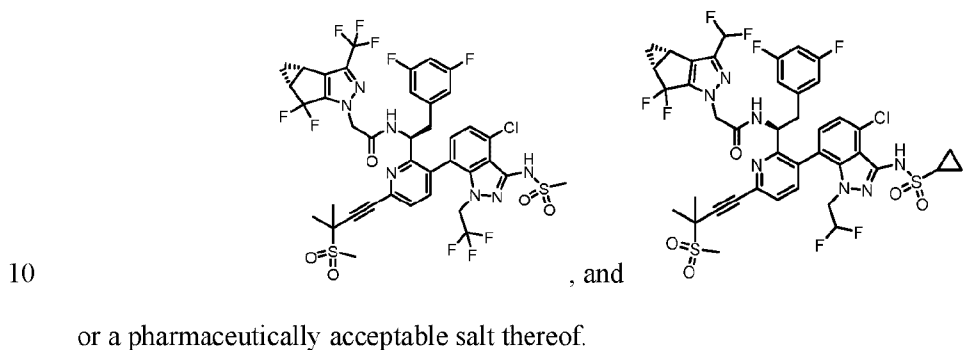
In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir
30 alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine.

In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with a capsid inhibitor(s) (e.g., capsid polymerization inhibitors and/or capsid disrupting compounds).

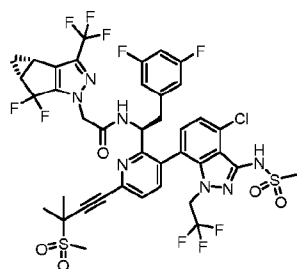
In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with (about 10 to about 1000 mg) of a capsid inhibitor selected from:



In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with a capsid inhibitor selected from:

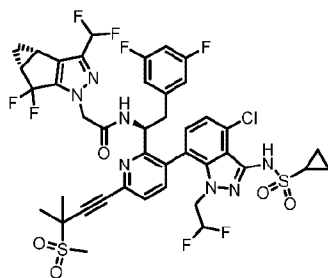


In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with:



, or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with:



, or a pharmaceutically acceptable salt thereof.

- 5 A compound as disclosed herein (e.g., any compound of Formula (I)) may be combined with one or more additional therapeutic agents in any dosage amount of the compound of Formula (I) (e.g., from 1 mg to 1000 mg of compound).

- In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 5-30 mg tenofovir alafenamide, in the form of tenofovir
- 10 alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, or any salt or solvate form of tenofovir alafenamide. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 5-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200
- 15 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 5-10, 5-15, 5-20, 5-25, 25-30, 20-30, 15-30, or 10-30
- 20 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 10 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg
- emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. A compound as

disclosed herein (e.g., a compound of formula (I)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 1 mg to 1000 mg of compound) the same as if each combination of dosages were specifically and individually listed.

In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 200-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 200-250, 200-300, 200-350, 250-350, 250-400, 350-400, 300-400, or 250-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 300 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of formula (I)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 1 mg to 1000 mg of compound) the same as if each combination of dosages were specifically and individually listed.

In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with a HIV nucleoside or nucleotide inhibitor and an integrase inhibitor. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with GS-9131 and bictegravir.

In one embodiment, kits comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents are provided.

Birth control (contraceptive) combination therapy

Therapeutic agents used for birth control (contraceptive) include cyproterone acetate, desogestrel, dienogest, drospirenone, estradiol valerate, ethinyl Estradiol, ethynodiol, etonogestrel, levomefolate, levonorgestrel, lynestrenol, medroxyprogesterone acetate, mestranol, mifepristone, misoprostol, norgestrol acetate, norelgestromin, norethindrone, noretynodrel, norgestimate, ormeloxifene, segestersonone acetate, ulipristal acetate, and any combinations thereof.

30

Gene Therapy and Cell Therapy

Gene Therapy and Cell Therapy including the genetic modification to silence a gene; genetic approaches to directly kill the infected cells; the infusion of immune cells designed to replace most of the patient's own immune system to enhance the immune response to infected cells, or activate the patient's own immune system to kill infected cells, or find and kill the infected cells; genetic approaches to modify cellular activity to further alter endogenous immune responsiveness against the infection.

Examples of dendritic cell therapy include AGS-004.

Gene Editors

The genome editing system is selected from the group consisting of: a CRISPR/Cas9 system, a zinc finger nuclease system, a TALEN system, a homing endonucleases system, and a meganuclease system.

Examples of HIV targeting CRISPR/Cas9 systems include EBT101.

CAR-T cell therapy

A population of immune effector cells engineered to express a chimeric antigen receptor (CAR), wherein the CAR comprises an HIV antigen-binding domain. The HIV antigen include an HIV envelope protein or a portion thereof, gp120 or a portion thereof, a CD4 binding site on gp120, the CD4-induced binding site on gp120, N glycan on gp120, the V2 of gp120, the membrane proximal region on gp41. The immune effector cell is a T cell or an NK cell. In some embodiments, the T cell is a CD4⁺ T cell, a CD8⁺ T cell, or a combination thereof.

Examples of HIV CAR-T include VC-CAR-T.

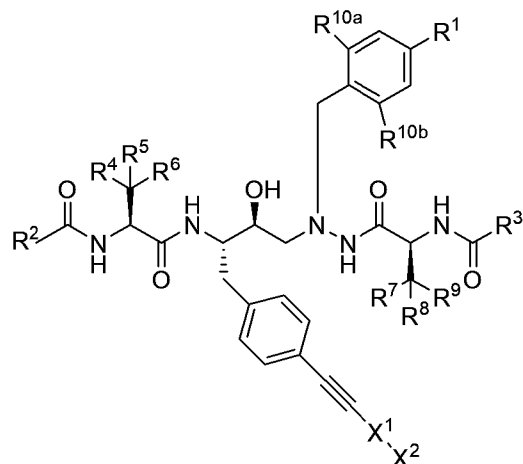
TCR-T cell therapy

TCR-T cells are engineered to target HIV derived peptides present on the surface of virus-infected cells.

Certain embodiments of the methods disclosed herein exclude the administration of a pharmacokinetic enhancer. For example, in certain methods disclosed herein, the subject is not administered a pharmacokinetic enhancer, such as cobicistat or ritonavir, during the treatment with a compound disclosed herein, or a pharmaceutically acceptable salt thereof. Thus, in certain embodiments, a method of treating or preventing a human immunodeficiency virus (HIV)

infection is provided, comprising administering a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein the treatment does not comprise administration of a pharmacokinetic enhancer. In certain embodiments, a method of treating or preventing a human immunodeficiency virus (HIV) infection is provided, comprising administering a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, once daily to a subject in need thereof, wherein the treatment does not comprise administration of a pharmacokinetic enhancer.

The present disclosure provides a compound of Formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is a 5 to 10-membered heterocycle having 1 to 5 heteroatoms selected from N, O, and S, or a 5 to 10-membered heteroaryl having 1 to 5 heteroatoms selected from N, O, and S, wherein the 5 to 10-membered heterocycle or 5 to 10-membered heteroaryl is optionally substituted with 1 to 5 R^a groups;

R² and R³ are each independently C₁₋₄alkyl, C₃₋₆cycloalkyl, O-R^{2A}, C₁₋₂alkyl-O-R^{2A}, N-(R^{3A})₂, or C₁₋₂alkyl-N-(R^{3A})₂,

wherein each R^{2A} is independently C₁₋₄alkyl, C₃₋₆cycloalkyl, or a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S,

wherein each R^{3A} is independently hydrogen, C₁₋₄alkyl, C₃₋₆cycloalkyl, or COO(R^c),

and wherein each C₃₋₆cycloalkyl or 4 to 10-membered heterocyclyl is optionally substituted by 1 to 3 R^f groups, wherein each R^f is independently C₁₋₂alkyl or halogen;

- R⁴ is C₁₋₄alkyl or C₁₋₄haloalkyl;
 R⁷ is C₁₋₄alkyl or C₁₋₄haloalkyl;
 R⁵, R⁶, R⁸, and R⁹ are each independently C₁₋₂alkyl or C₁₋₂haloalkyl;
 and wherein two or more of R⁴, R⁵ and R⁶ or two or more of R⁷, R⁸, and R⁹
 5 optionally join together to form one or more C₃₋₆cycloalkyl groups that are
 optionally substituted with 1 to 4 groups selected from halogen, C₁₋₂alkyl, and C₁₋₂haloalkyl;
 R^{10a} and R^{10b} are halogen;
- 10 each R^a is independently halogen, C₁₋₄alkyl, C₁₋₄alkyl substituted with 1 to 2 groups selected
 from hydroxyl and C₁₋₄alkoxy, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₃₋₆cycloalkyl, 4 to 10-
 membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S which is
 optionally substituted with R^{a1}, or O-R^{3B},
 wherein R^{3B} is C₃₋₆cycloalkyl optionally substituted with R^{a1} or a 4 to 10-
 15 membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S
 optionally substituted with R^{a1},
 wherein each R^{a1} is independently C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄haloalkyl, or 4
 to 8-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S;
- X¹ is a 6 to 10-membered aryl or a 5 to 10-membered heteroaryl having 1 to 3 heteroatoms
 20 selected from N, O, and S, wherein each 6 to 10-membered aryl or 5 to 10-membered
 heteroaryl is optionally substituted with 1 to 4 R^b groups;
- X² is hydrogen or a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N,
 O, and S, wherein the 4 to 10-membered heterocyclyl is optionally substituted with one
 R¹¹ and optionally substituted with 1 to 5 R^b groups;
- 25 R¹¹ is C=O(R^c), CH₂(R^d), S(O)₁₋₂(C₁₋₄alkyl), S(O)₁₋₂C₃₋₆cycloalkyl, a 4 to 10-membered
 heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S, or a 5 to 9-membered
 heteroaryl having 1 to 5 heteroatoms selected from N, O, and S, wherein each 4 to 10-
 membered heterocyclyl or 5 to 9-membered heteroaryl is optionally substituted with 1 to
 5 R^b groups;
- 30 each R^b is independently halogen, oxo, C₁₋₄alkyl, C₁₋₄alkyl substituted with 1 to 2
 groups selected from hydroxyl and C₁₋₄alkoxy, C₁₋₄haloalkyl, C₁₋₄alkoxy,
 or COO(R^c);
 R^c is C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, N(R^c)₂, C₃₋₆cycloalkyl, or a 4 to 6-
 membered heterocyclyl having 1 to 3 heteroatoms selected from N, O,

and S, wherein the C₃₋₆ cycloalkyl and the 4 to 6-membered heterocyclyl are optionally substituted by 1 to 5 R^b groups;

R^d is COO(R^c), N(R^c)₂, C₃₋₆ cycloalkyl, or a 4 to 6-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S, wherein the C₃₋₆ cycloalkyl and the 4 to 6-membered heterocyclyl is optionally substituted by 1 to 5 R^b groups;

and each R^c is independently hydrogen or C₁₋₄alkyl.

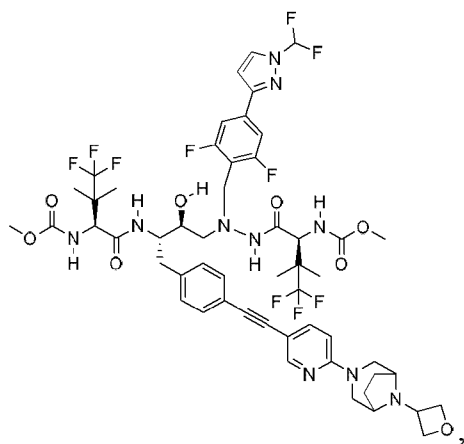
The present disclosure provides a compound or pharmaceutically acceptable salt thereof as defined herein, or the pharmaceutical composition as defined herein, for use in the treatment of a human immunodeficiency virus (HIV) infection.

The present disclosure provides a compound or pharmaceutically acceptable salt thereof as defined herein, or the pharmaceutical composition as defined herein, for use in the manufacture of a medicament for the treatment of a human immunodeficiency virus (HIV) infection.

The present disclosure provides the use of the compound or pharmaceutically acceptable salt as defined herein, or the pharmaceutical composition as defined herein, for the manufacture of a medicament for the treatment of a human immunodeficiency virus (HIV) infection.

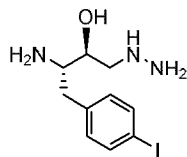
The present disclosure provides the use of the of the compound or pharmaceutically acceptable salt thereof as defined herein, or the pharmaceutical composition as defined herein, for the treatment of a human immunodeficiency virus (HIV) infection.

The present disclosure provides a process for preparing compound:



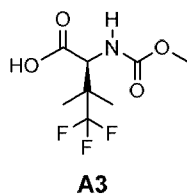
or a pharmaceutically acceptable salt thereof, comprising:

a) reacting deprotected Compound I2a:

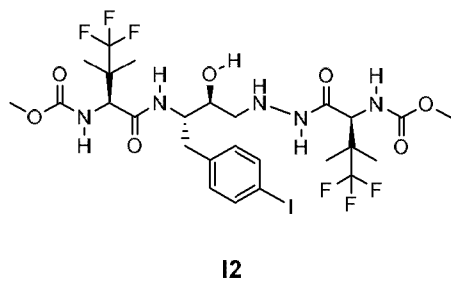


5

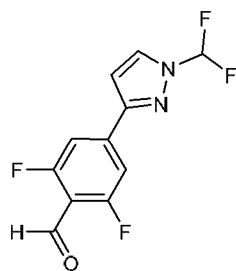
with Compound A3:



to provide Compound I2:

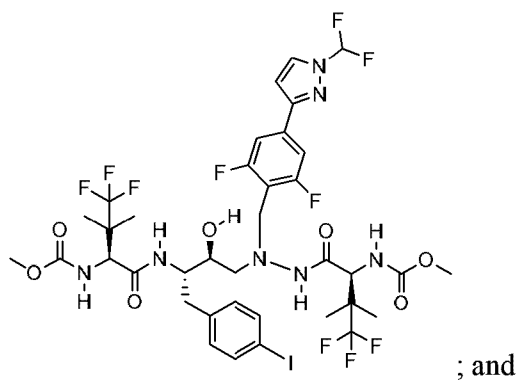


b) reacting Compound I2 with Compound P4:



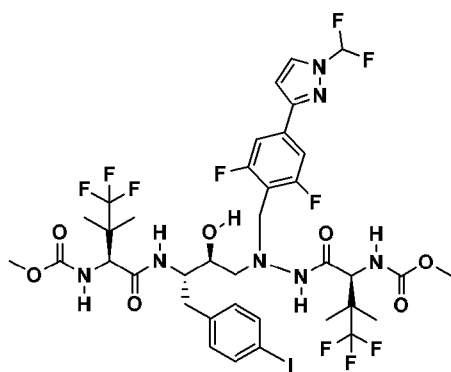
P4

to provide a compound of structure:



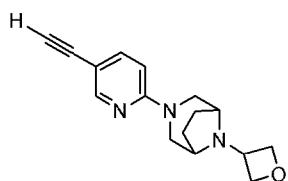
; and

c) reacting a compound of structure:



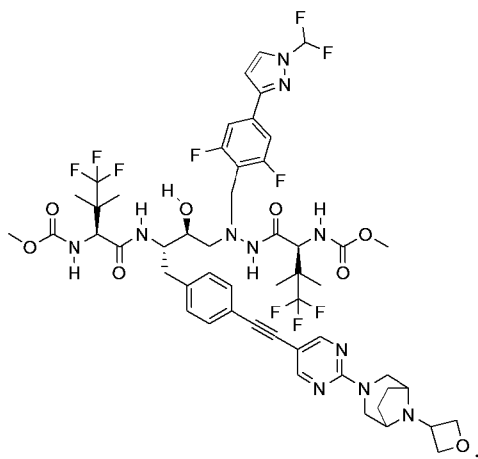
5

with Compound S3:



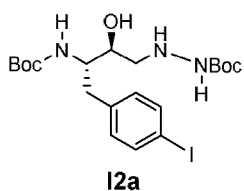
S3

The present disclosure provides a process for preparing compound:



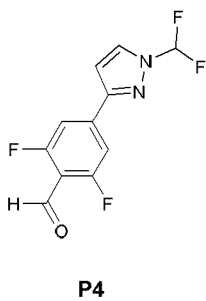
or a pharmaceutically acceptable salt thereof, comprising:

a) reacting Compound I2a:

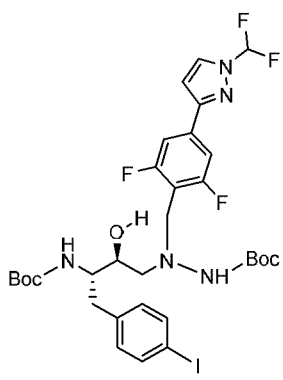


5

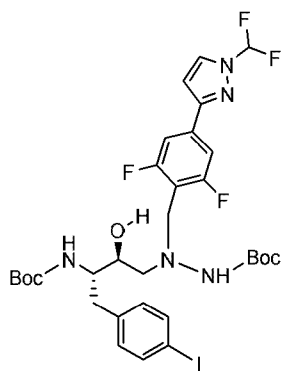
with Compound P4:



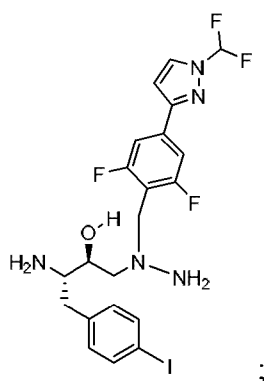
to provide a compound of structure:



b) deprotecting a compound of structure:

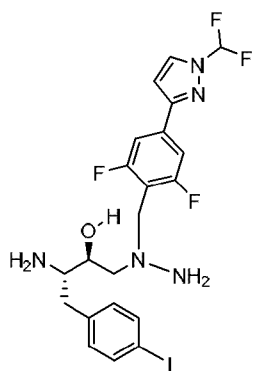


with HCl to provide a compound of structure:

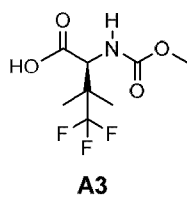


5

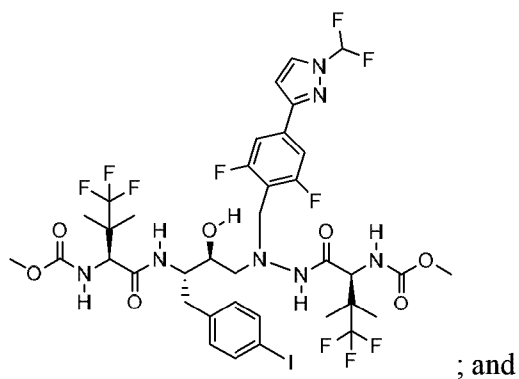
c) reacting a compound of structure:



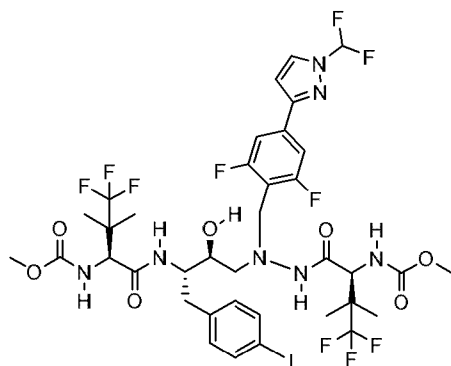
with Compound A3:



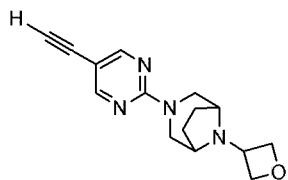
to provide a compound of structure:



d) reacting a compound of structure:



with Compound S7:



S7

5

The present disclosure also provides all of the P, S, A and I intermediates described in the Examples section below.

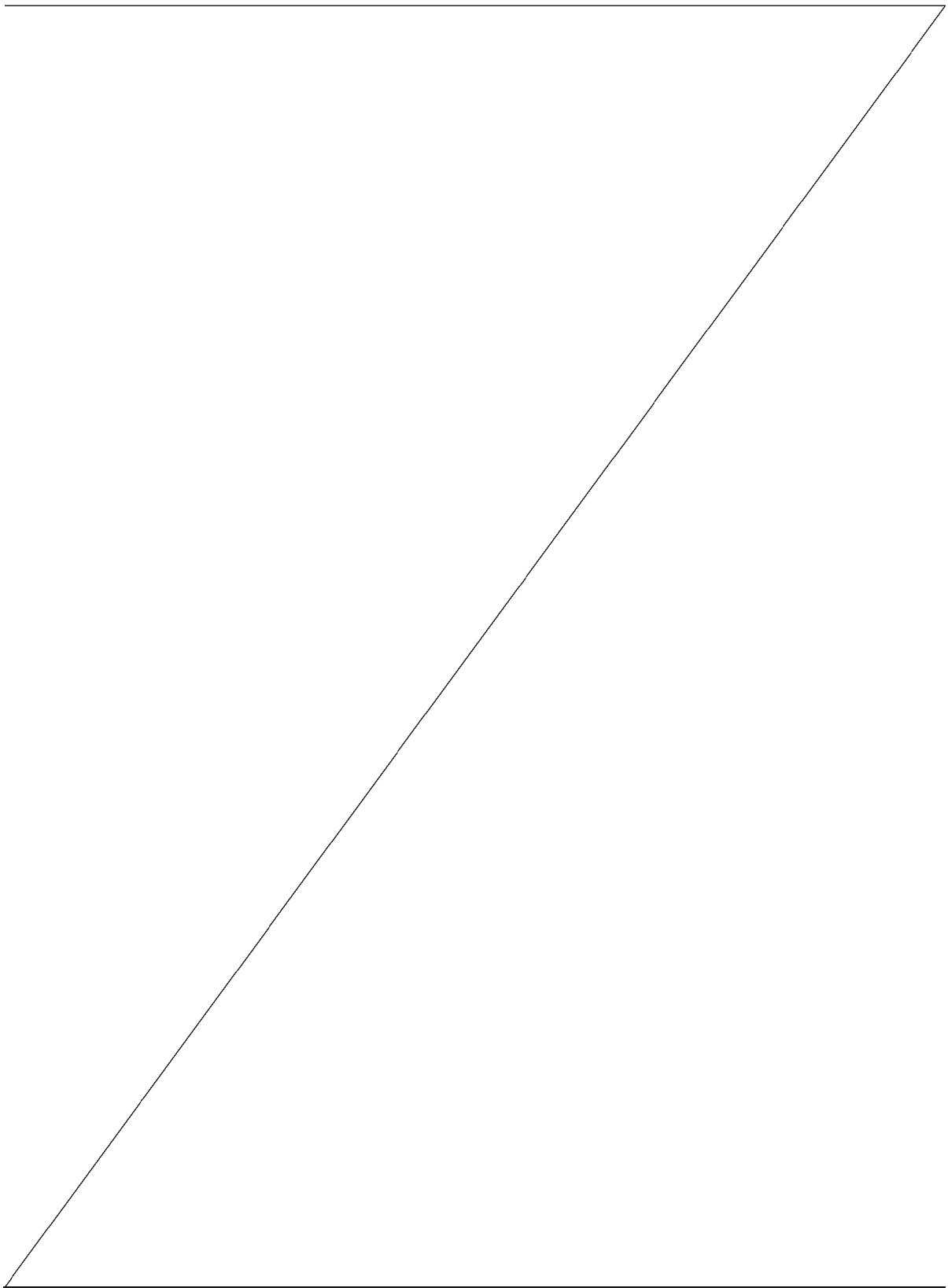
10 EXAMPLES

Methods for preparing the novel compounds described herein will be apparent to those of skill in the art with suitable procedures being described, for example, in the reaction schemes and examples below.

Sections 1.1 – 1.8 provide exemplary synthetic schemes for assembling compounds of Formula I. Sections 2.1 – 2.4 show preparation of Intermediate I, Intermediate P, Intermediate S, and Intermediate A, as used herein. Section 3 provides example syntheses and compounds.

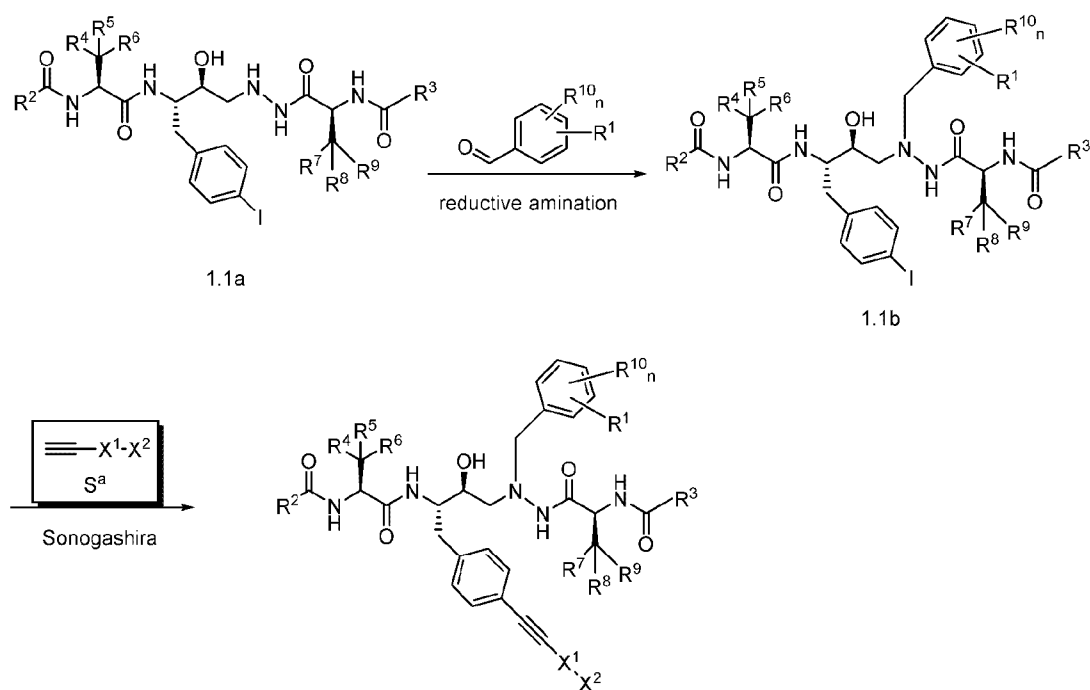
15

Section 4 shows biological activity.

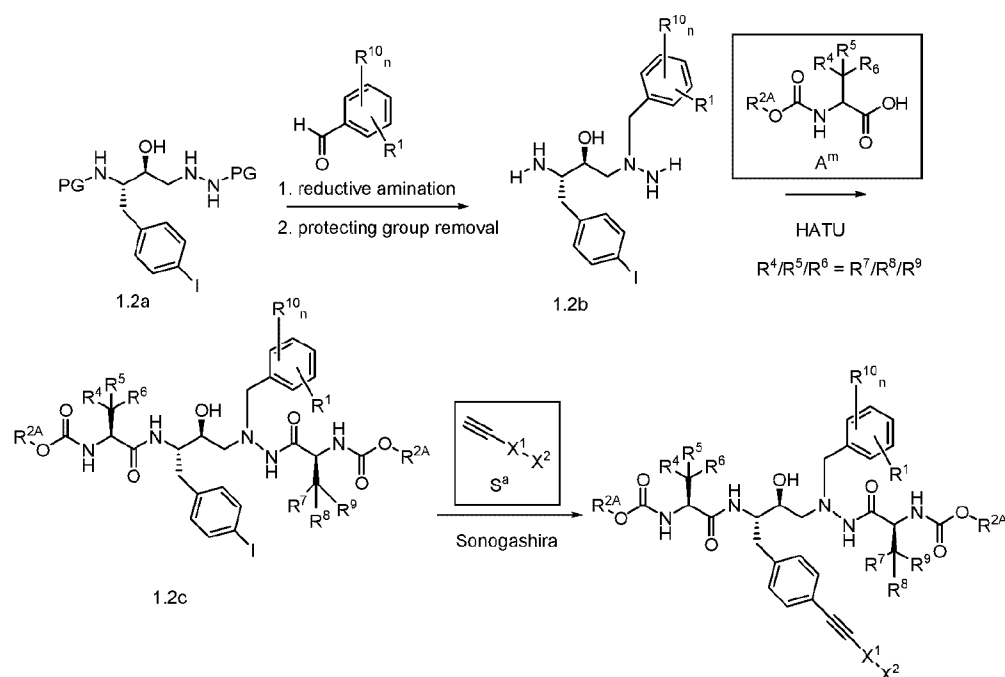


1. General Schemes

SCHEME 1.1



- Scheme 1.1 shows a general synthesis of a compound within the scope of Formula I
- 5 beginning with reductive amination of compound 1.1a with a substituted benzaldehyde (Intermediate P). Reductive amination may be accomplished, for example, with a cyanoborohydride reagent such as sodium cyanoborohydride. Subsequent metal-catalyzed coupling such as Sonogashira- or Suzuki-couplings. Sonogashira coupling of compound 1.1b with an alkynyl Intermediate S^a gives a compound of Formula I.
- 10 Examples 1-130, 219, and 224-245 were prepared by this general strategy (by reductive amination of the appropriate Intermediate P with the corresponding organohalide peptide Intermediate I, followed by Sonogashira coupling with the appropriate Intermediate S).
- Example 1 provides exemplary reaction conditions and reagents appropriate for preparing a compound of Formula I according to Scheme 1.1.

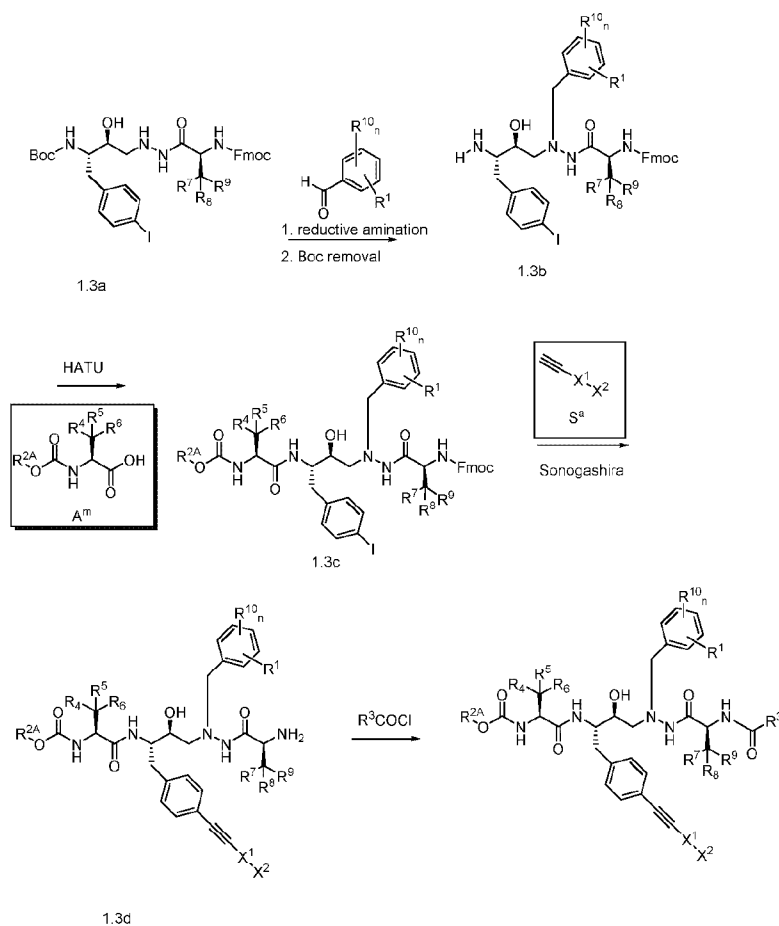
SCHEME 1.2

Scheme 1.2 shows a general synthesis of a compound within the scope of Formula I with reductive amination of a protected amino hydrazinyl iodophenyl butanol, compound 1.2a.

- 5 Exemplary protecting groups (PG) for compound 1.2a include *t*-butylcarbonyl (BOC) protecting group and fluorenylmethyloxycarbonyl (Fmoc). Reductive amination of compound 1.2a with a substituted benzaldehyde Intermediate P gives compound 1.2b after removal of the protecting groups. Reductive amination may be accomplished, by way of non-limiting example, with sodium cyanoborohydride. HATU coupling of compound 1.2b with an amino acid Intermediate A^m gives a compound 1.2c. Sonogashira coupling of compound 1.2c with an alkynyl Intermediate S^a gives a compound of Formula I.

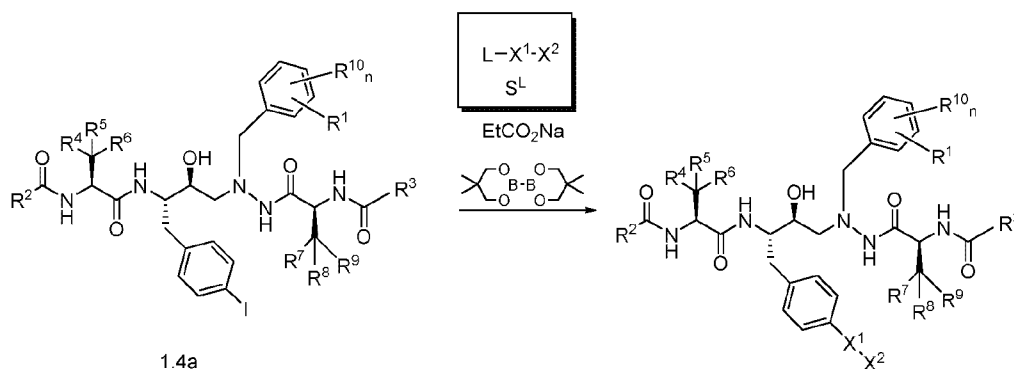
Examples 133-180 and 220 were prepared by this general strategy (reductive amination of the appropriate P with an amino hydrazinyl iodophenyl butanol followed by HATU coupling A^m, which is then followed by Sonogashira coupling with an alkynyl Intermediate S^a).

- 15 Example 133 provides exemplary reaction conditions and reagents appropriate for preparing a compound of Formula I according to Scheme 1.2.

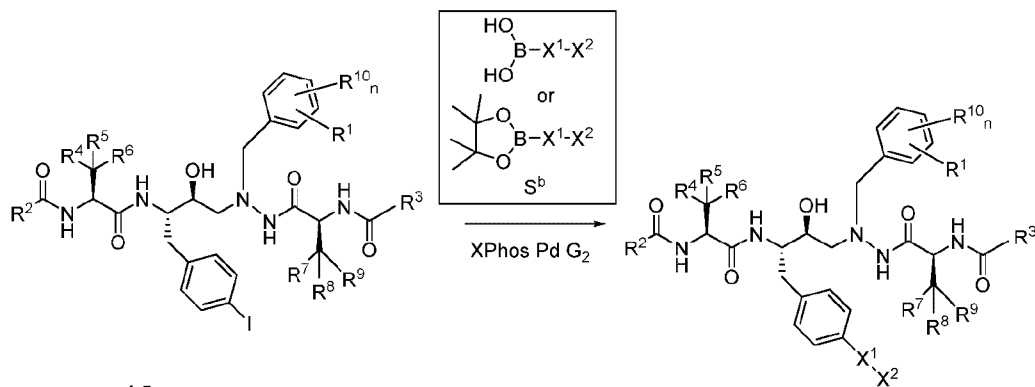
SCHEME 1.3

Scheme 1.3 shows a general synthesis of a compound within the scope of Formula I beginning with reductive amination of a protected organohalide compound 1.3a with a benzaldehyde Intermediate P and Boc removal to give compound 1.3b. Reductive amination may be accomplished, by way of non-limiting example, with sodium cyanoborohydride. Boc removal may be accomplished, by way of non-limiting examples, with trifluoroacetic acid or hydrochloric acid. HATU coupling of compound 1.3b with an amino acid Intermediate A^m gives the intermediate peptide 1.3c. Sonogashira coupling of the intermediate peptide 1.3c and an alkynyl Intermediate S gives intermediate 1.3d. Subsequent reaction of compound 1.3d with an acyl chloride gives a compound of Formula I.

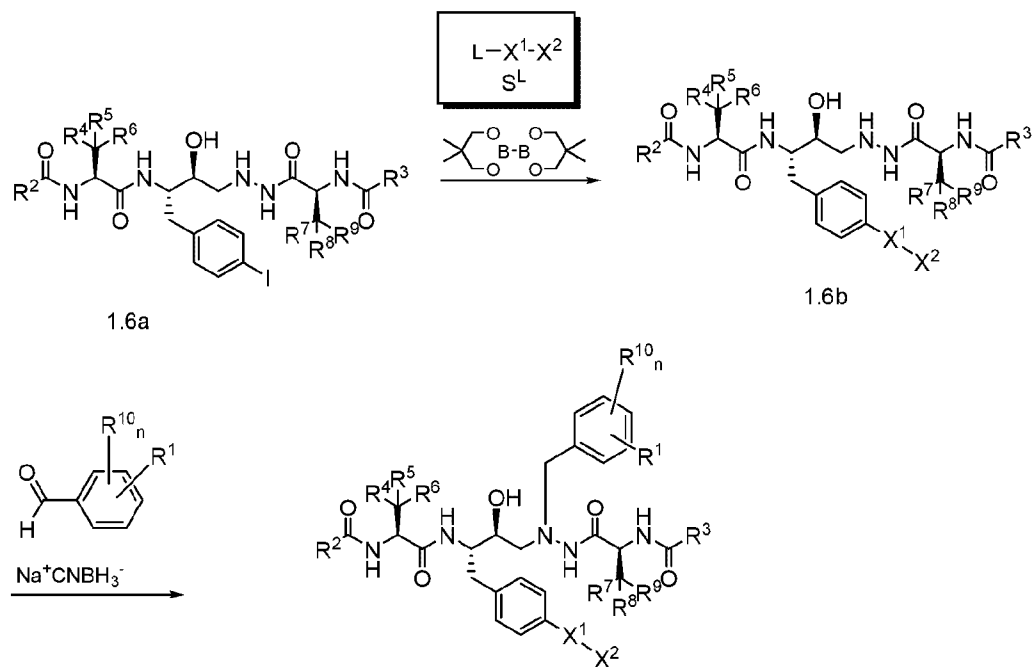
Examples 183-186 were prepared by this general strategy. Example 183 provides exemplary reaction conditions and reagents appropriate for preparing a compound of the invention according to Scheme 1.3.

SCHEME 1.4

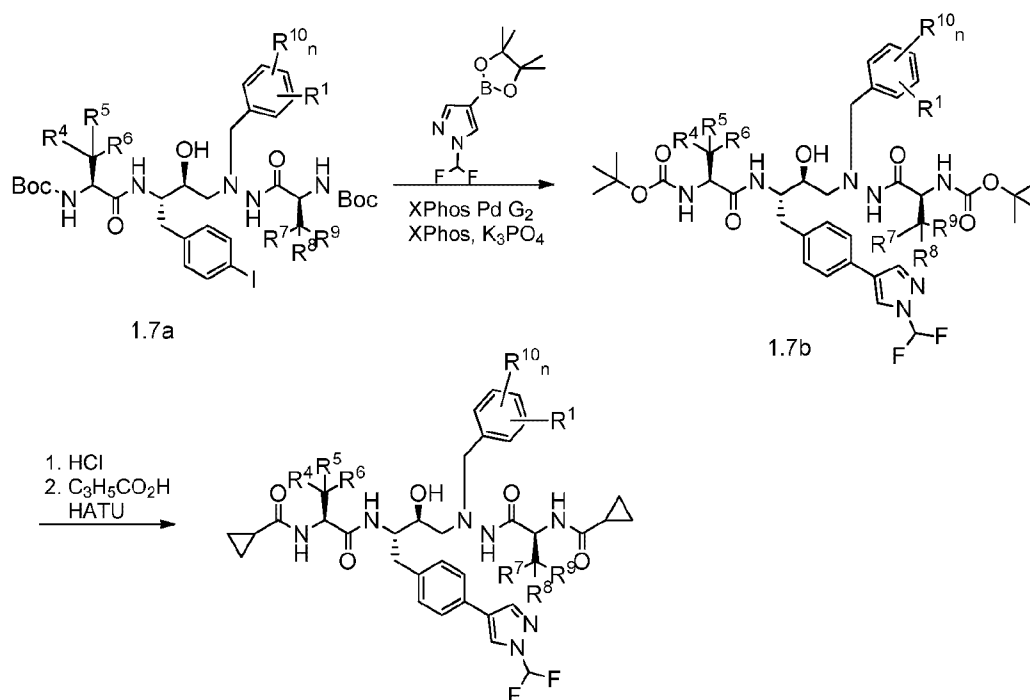
X^1 may be installed directly on the halophenyl as exemplified in Scheme 1.4. In this example, an organohalide Intermediate S^L (shown above where L is iodo, bromo, or chloro) is coupled with compound 1.4a by Borylation-Suzuki reaction. Examples 188-201 were prepared using the methodology shown in Scheme 1.4. Exemplary reaction conditions are found in Example 188.

SCHEME 1.5

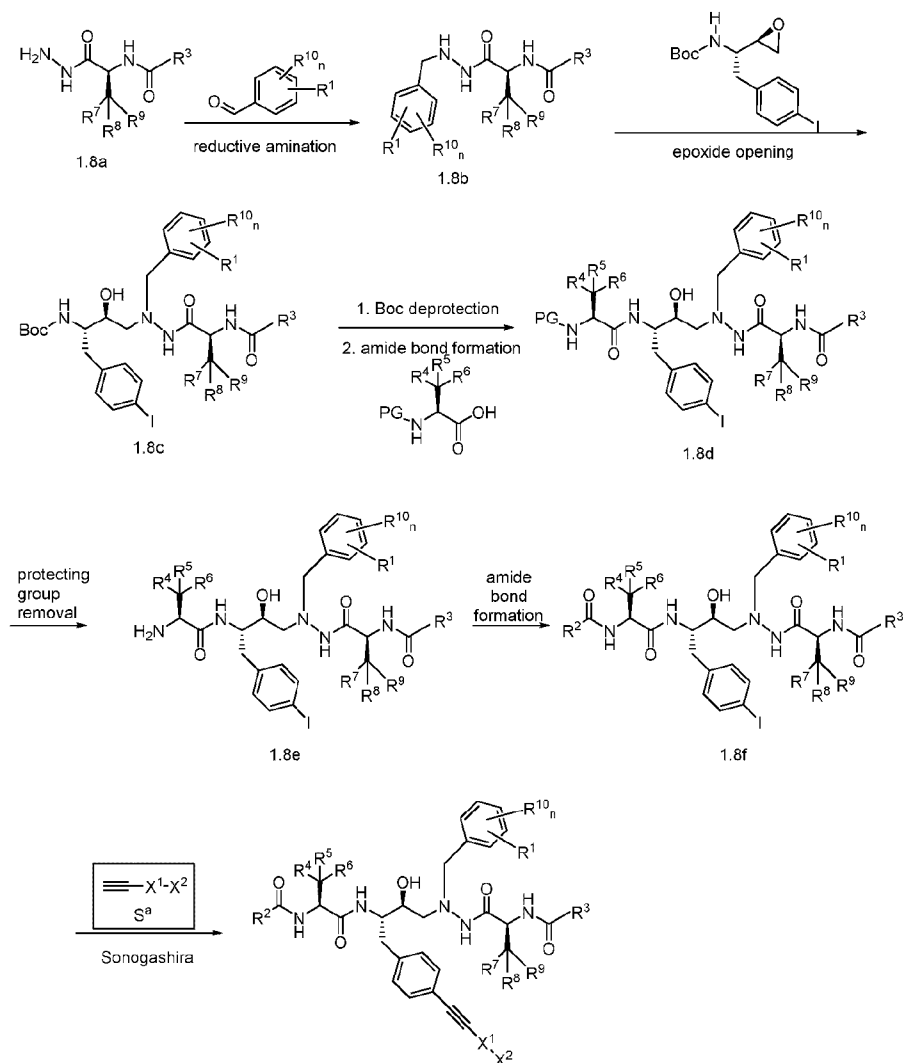
Alternatively, X^1 may be installed by metal catalyzed coupling of a boronic acid or boronic ester (Intermediate S^b) with compound 1.5a. The reaction is conducted with XPhos Pd G_2 . Xphos is also known as XPhos is 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl. Pd G_2 is chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II). Examples 202-211 and 218 were prepared according to Scheme 1.5. Example 202 provides exemplary reaction conditions for this transformation.

SCHEME 1.6

Example 212 was made in according to Scheme 1.6. Example 212 provides exemplary reaction conditions for transformations according to Scheme 1.6.

SCHEME 1.7

- 5 Scheme 1.7 shows an example of a Suzuki cross coupling, followed by Boc-deprotection and amide bond formation. Exemplary reaction conditions can be found in Example 213. Examples 214-217 show installation of different R² and R³ groups using the same general strategy and the appropriate acid chloride.

SCHEME 1.8

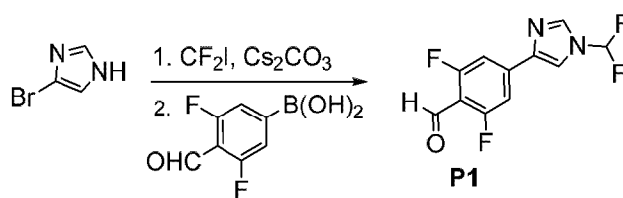
- Scheme 1.8 shows a general synthesis of a compound within the scope of Formula I beginning
- 5 with reductive amination of compound 1.8a with a substituted benzaldehyde (Intermediate P). Reductive amination of compound 1.8a with a substituted benzaldehyde Intermediate P gives compound 1.8b. Reductive amination may be accomplished, by way of non-limiting example, with sodium cyanoborohydride. Subsequent epoxide opening of tert-butyl ((S)-2-(4-
- 10 iodophenyl)-1-((R)-oxiran-2-yl)ethyl)carbamate give compound 1.8c. Subsequent Boc removal followed by Subsequent amide bond formation gives compound 1.8d. Boc removal may be accomplished, by way of non-limiting examples, with trifluoroacetic acid or hydrochloric acid. Amide bond formation may be accomplished, by way of non-limiting example, with a

carboxylic acid and a reagent, such as HATU. Subsequent protecting group removal gives compound 1.8e. Subsequent amide bond formation gives compound 1.8f. Amide bond formation may be accomplished, by way of non-limiting example, with a carboxylic acid and a reagent, such as HATU. Subsequently metal-catalyzed coupling such as Sonogashira- or Suzuki-couplings may be performed. Sonogashira coupling of compound 1.8d with an alkynyl Intermediate S^a gives a compound of Formula I.

Examples 221-223 were prepared by this general strategy.

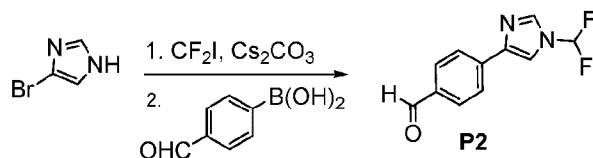
2. Synthesis of Intermediates

10 2.1 SYNTHESIS OF P INTERMEDIATES



4-(1-(difluoromethyl)-1H-imidazol-4-yl)-2,6-difluorobenzaldehyde (P1). A suspension of 4-bromo-1H-imidazole (1 g, 6.8 mmol) cesium carbonate (44430 mg, 136.36 mmol), and difluoroiodomethane (10% wt. in THF, 20 ml, 10.62 mmol) in a 75mL sealed vessel was heated at 50°C overnight. The reaction mixture was cooled to room temperature and then filtered through Celite™. The filter cake was washed with EtOAc. The filtrate was washed with brine, dried over sodium sulfate and carefully concentrated. The residue was purified by silica column chromatography (17% to 47% EtOAc/Hex) to give 1.3g of a mixture of regioisomers. This mixture was combined with 3,5-Difluoro-4-formylphenylboronic acid (1.6 g, 8.58 mmol), XPhos Pd G2 (0.4 g, 0.26 mmol), 2-(Dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (0.12 g, 0.26 mmol), Potassium phosphate tribasic (2 M, 3.3 ml) in dioxane (11 ml) and degassed for 10 min with argon, then heated at 100 °C overnight. The reaction mixture was cooled to room temperature, concentrated under reduce pressure, the residue was diluted with EtOAc and washed with brine 2x then dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (23% to 92% EtOAc/Hex) to give the desired isomer **P1**. MS (ESI) m/z 259.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ

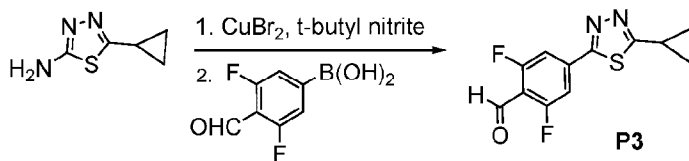
10.32 (d, J = 1.1 Hz, 1H), 7.91 (d, J = 1.3 Hz, 1H), 7.63 (d, J = 1.3 Hz, 1H), 7.48 - 7.36 (m, 2H), 7.16 (t, J = 60.8 Hz, 1H).



5

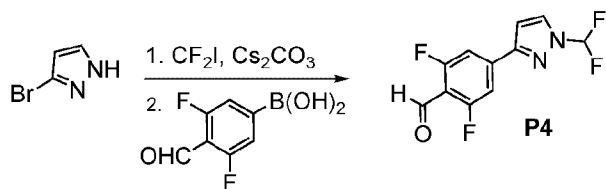
4-(1-(difluoromethyl)-1H-imidazol-4-yl)benzaldehyde (P2). The title compound **P2** was prepared according to the method presented for the synthesis of intermediate **P1** but instead utilizing (4-formylphenyl)boronic acid. MS (ESI) m/z 223.2 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 10.02 (s, 1H), 8.01 - 7.89 (m, 5H), 7.62 (d, J = 1.3 Hz, 1H), 7.15 (t, J = 60.9

10 Hz, 1H).

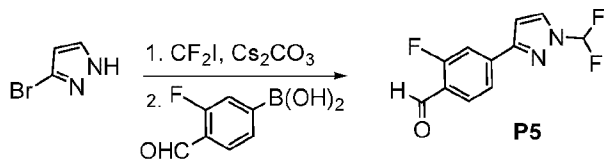


4-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-2,6-difluorobenzaldehyde (P3). To a heterogeneous solution of Cupric bromide (3.8 g, 17 mmol) and tert-Butyl nitrite (2.53 ml, 21.25 mmol) in MeCN (78 mL) in a 3 neck flask charged with a stir bar, side arm inlet, under argon, was added 5-cyclopropyl-1,3,4-thiadiazol-2-amine (2 g, 14.16 mmol) slowly due to exothermic reaction, and stirred at room temperature under argon overnight. The reaction mixture was quenched with 78 mL of saturated NH_4Cl (aq) and extracted with diethyl ether and the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by silica column chromatography (10% to 50% EtOAc/Hex). The product (0.28 g, 1.34 mmol) was combined with 3,5-Difluoro-4-formylphenylboronic acid (0.5 g, 2.69 mmol), XPhos Pd G2 (0.15 g, 0.09 mmol), 2-(Dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (45.06 mg, 0.09 mmol), potassium phosphate tribasic (2 M, 1.34 ml) in dioxane (4.9 ml) and degassed for 10 min with argon, then heated at 100 °C overnight. The reaction mixture was cooled to room temperature, concentrated under reduce pressure, the residue was diluted with EtOAc and washed with brine 2x then dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (21% to 100%EtOAc/Hex) to

give the desired isomer **P3**. MS (ESI) m/z 267.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 10.37 (s, 1H), 7.56 (d, J = 9.0 Hz, 2H), 5.30 (d, J = 0.7 Hz, 0H), 2.47 (dt, J = 8.1, 3.7 Hz, 1H), 1.55 (s, 5H), 1.33 (dd, J = 8.3, 4.1 Hz, 2H), 1.26 (d, J = 4.4 Hz, 5H), 0.92 - 0.79 (m, 2H).

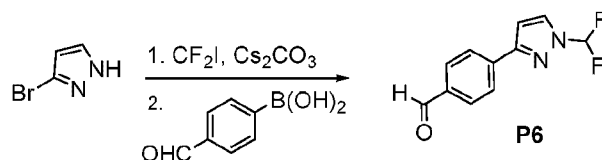


5
Synthesis of 4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzaldehyde (P4) In a 150 mL pressure vessel, a suspension of 3-bromo-1H-pyrazole (8 g, 54.43 mmol) cesium carbonate (53.2 g, 163.29 mmol), and diiododifluoromethane (10% wt. in THF, 200 ml, 106.23 mmol) was heated at 45°C overnight. The reaction mixture was cooled to room temperature and then filtered through Celite. The filter cake was washed with Et_2O (3 x 150 mL). The filtrate was washed with brine, dried over sodium sulfate and carefully concentrated (20 °C bath, 100 mb vacuum) to give ~17 g of a 1.5:1 ratio of regioisomers and solvent still present. This crude material was combined with 3,5-Difluoro-4-formylphenylboronic acid (12.65 g, 68.03 mmol),
 15 Palladium acetate (0.31 g, 1.381 mmol), butyldi-1-adamantylphosphine (1.171 g, 3.265 mmol) and Potassium carbonate (22.80 g, 164.96 mmol) in dioxane (150 mL) and water (50 mL) the mixture was degassed for 10 min with argon, then heated at 100 °C overnight. The reaction mixture was cooled to room temperature, concentrated under reduce pressure, the residue was diluted with EtOAc and washed with brine 2x then dried over Na_2SO_4 , filtered and concentrated
 20 under reduced pressure. The crude residue was purified by silica column chromatography (5% to 15% EtOAc/Hex). Mixed fractions were recrystallized (5:1 Hex/EtOAc) combined pure product afforded **P4**. 1H NMR (400 MHz, Chloroform- d) δ 10.35 (d, J = 1.0 Hz, 1H), 7.92 (d, J = 2.8 Hz, 1H), 7.46 (d, J = 9.6 Hz, 2H), 7.24 (t, J = 60.5 Hz, 1H), 6.80 (d, J = 2.8 Hz, 1H).

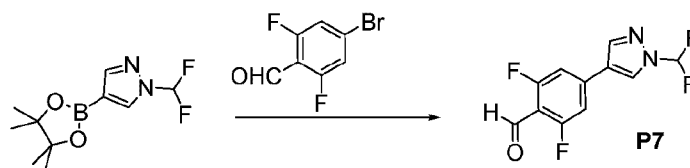


25 **Synthesis of 4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluorobenzaldehyde (P5).** The title compound **P5** was prepared according to the method presented for the synthesis of intermediate **P4** but instead utilizing (3-fluoro-4-formylphenyl)boronic acid. 1H NMR (400 MHz,

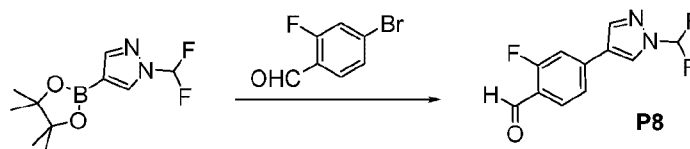
Chloroform-*d*) δ 10.41 (s, 1H), 7.97 (dd, $J = 8.0, 7.1$ Hz, 1H), 7.71 (d, $J = 1.7$ Hz, 1H), 7.50 – 7.34 (m, 2H), 6.55 (d, $J = 1.7$ Hz, 1H).



- 5 **Synthesis of 4-(1-(difluoromethyl)-1H-pyrazol-3-yl)benzaldehyde (P6).** The title compound **P6** was prepared according to the method presented for the synthesis of intermediate **P4** but instead utilizing (4-formylphenyl)boronic acid. ^1H NMR (400 MHz, Chloroform-*d*) δ 10.05 (s, 1H), 8.03 – 7.93 (m, 4H), 7.90 (d, $J = 2.7$ Hz, 1H), 6.85 (d, $J = 2.7$ Hz, 1H).

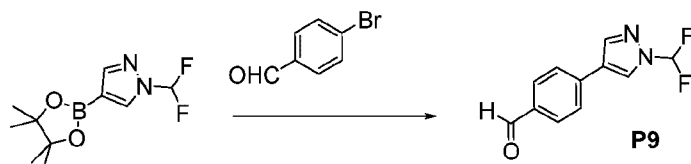


- 10 **Synthesis of 4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzaldehyde (P7).** A suspension of 1-Difluoromethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (1.47 g, 6.03 mmol), 4-bromo-2,6-difluorobenzaldehyde (1.1 g, 4.98 mmol), palladium acetate (0.03 g, 0.12 mmol), butyldi-1-adamantylphosphine (0.11 g, 0.3 mmol), and potassium carbonate (2.06 g, 14.93 mmol) in water (7 ml) and 1,4-dioxane (22 ml) in a tube was degassed
- 15 for 10 min with argon, then the tube was sealed and heated at 100 °C overnight. The reaction mixture was cooled to room temperature, concentrated under reduce pressure, the residue was diluted with EtOAc and washed with brine 2x then dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (10% to 25% EtOAc/Hex) to afford **P7**. ^1H NMR (400 MHz, Chloroform-*d*) δ 10.32 (s, 1H), 8.16 (s, 1H), 7.96 (s, 1H), 7.23 (t, $J = 60.4$ Hz, 1H), 7.14 (d, $J = 9.5$ Hz, 2H).
- 20



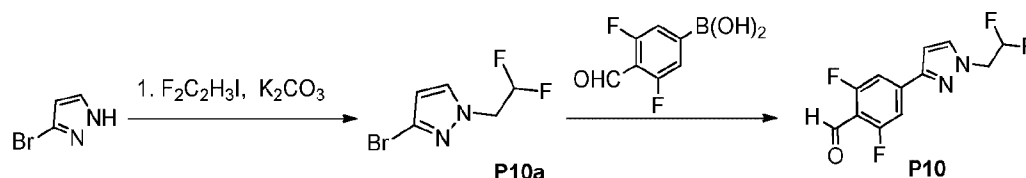
- Synthesis of 4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluorobenzaldehyde (P8).** The title compound **P8** was prepared according to the method presented for the synthesis of intermediate
- 25 **P7** but instead utilizing 4-bromo-2-fluorobenzaldehyde. ^1H NMR (400 MHz, Chloroform-*d*) δ

10.35 (d, $J = 0.7$ Hz, 1H), 8.15 (d, $J = 0.7$ Hz, 1H), 7.98 (q, $J = 0.8$ Hz, 1H), 7.91 (dd, $J = 8.1$, 7.3 Hz, 1H), 7.42 (ddd, $J = 8.1$, 1.7, 0.8 Hz, 1H), 7.31 (dd, $J = 11.3$, 1.6 Hz, 1H), 7.23 (s, 1H).



Synthesis of 4-(1-(difluoromethyl)-1H-pyrazol-4-yl)benzaldehyde (P9). The title compound

- 5 **P9** was prepared according to the method presented for the synthesis of intermediate **P7** but instead utilizing 4-bromobenzaldehyde. ^1H NMR (400 MHz, Chloroform- d) δ 10.02 (s, 1H), 8.16 (s, 1H), 8.01 (d, $J = 0.8$ Hz, 1H), 7.96 – 7.90 (m, 2H), 7.71 – 7.66 (m, 2H), 7.24 (t, $J = 0.14$ Hz, 1H).



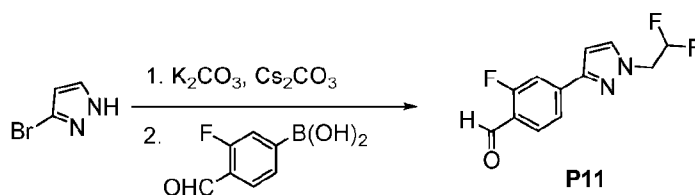
10

Synthesis of 3-bromo-1-(2,2-difluoroethyl)-1H-pyrazole (P10a) To a solution of 3-bromo-1H-pyrazole (6 g, 42.86 mmol) and Potassium carbonate (20.73 g, 150.03 mmol) in DMF (20 mL) at 35 °C, was added a solution of 1,1-difluoro-2-iodoethane (24.68 g, 128.59 mmol) dropwise via an addition funnel. The reaction was stirred overnight then cooled to room temperature,
 15 diluted with ether/hexanes and washed with brine and NH_4Cl solution. The organic layer was separated dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (7% to 25% EtOAc/Hex) to afford **P10a** (5.4 g 63.6%). MS (ESI) m/z 211.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 7.36 (d, $J = 2.4$ Hz, 1H), 6.32 (d, $J = 2.4$ Hz, 1H), 6.06 (tt, $J = 55.4$, 4.3 Hz, 1H), 4.41 (td, $J = 13.3$, 4.3 Hz,
 20 2H).

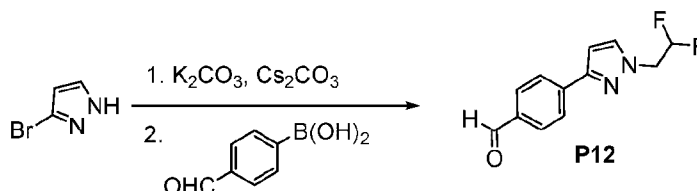
Synthesis of 4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzaldehyde (P10) **P10a**

- (4.31 g, 0.02 mol) was combined with 3,5-Difluoro-4-formylphenylboronic acid (4.96 g, 24.49 mmol), $\text{PdCl}_2(\text{tBu}_2\text{PPh})_2$ (570 mg, 0.92 mmol), and potassium phosphate tribasic monohydrate (1.0 M, 40.82 ml) in 2-methyltetrahydrofuran (20 mL) and water (20 mL) the mixture was
 25 degassed for 10 min with argon, then heated at 75°C overnight. The reaction was cooled to room temperature, the organic layer was separated and the aqueous layer was extracted into EtOAc. The combined organic layers were washed with 1M HCl, then brine, filter concentrated under reduce pressure, the residue was diluted with EtOAc and washed with brine 2x then dried over

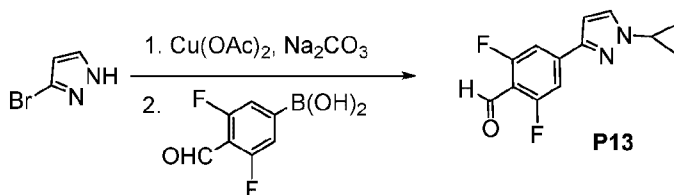
Na₂SO₄, filtered and concentrated under reduced pressure, recrystallized (1:3 EtOAc/ hexanes). The separated solids contained a mixture of desired isomer and unreacted boronic acid. This mixture was purified by silica column chromatography (70% to 100% DCM/Hex) to afford **P10** (2.3 g, 41%) MS (ESI) m/z 273.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 10.34 (d, J = 1.0 Hz, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.47 - 7.38 (m, 2H), 6.67 (d, J = 2.4 Hz, 1H), 6.15 (tt, J = 55.3, 4.3 Hz, 1H), 4.52 (td, J = 13.5, 4.3 Hz, 2H).



- 10 **Synthesis of 4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2-fluorobenzaldehyde (P11).** The title compound **P11** was prepared according to the method presented for the synthesis of intermediate **P10** but instead utilizing (3-fluoro-4-formylphenyl)boronic acid. ¹H NMR (400 MHz, Chloroform-d) δ 10.34 (d, J = 0.8 Hz, 1H), 7.89 (dd, J = 8.1, 7.2 Hz, 1H), 7.70 – 7.58 (m, 2H), 7.54 (d, J = 2.4 Hz, 1H), 7.33 (dt, J = 8.0, 1.0 Hz, 0H), 7.26 (dd, J = 10.7, 1.5 Hz, 0H), 6.68 (d, J = 2.4 Hz, 1H), 6.42 (d, J = 1.9 Hz, 0H), 6.15 (tt, J = 55.4, 4.3 Hz, 1H), 4.52 (td, J = 13.5, 4.3 Hz, 2H).



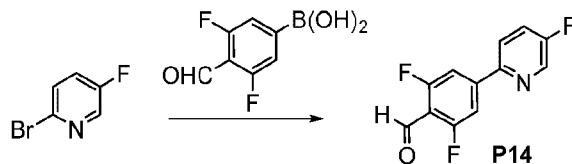
- Synthesis of 4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)benzaldehyde (P12).** The title compound **P12** was prepared according to the method presented for the synthesis of compound **P10** but instead utilizing (4-formylphenyl)boronic acid. MS (ESI) m/z 273.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 10.34 (d, J = 1.0 Hz, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.47 - 7.38 (m, 2H), 6.67 (d, J = 2.4 Hz, 1H), 6.15 (tt, J = 55.3, 4.3 Hz, 1H), 4.52 (td, J = 13.5, 4.3 Hz, 2H).



Synthesis of 4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzaldehyde (P13)

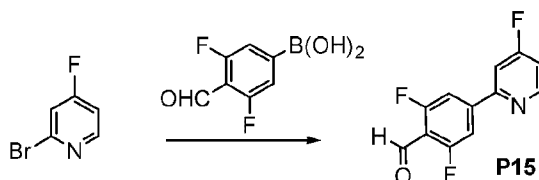
A suspension of copper(II) acetate anhydrous (3.7g, 20.41 mmol), and 2,2'-bipyridyl (3.2g, 20.41 mmol) in DCE (40 mL) was degassed, warmed to 50°C, and stirred for 10 minutes, before
 5 addition to 3-bromo-1H-Pyrazole (3 g, 20.41 mmol), cyclopropylboronic acid (5.3 g, 20.41) and sodium carbonate (4.8 g, 44.91 mmol) in DCE (60 mL). The reaction was stirred at 65 °C for 48 h. The reaction mixture was cool to room temperature, filtered through a Celite frit, and rinsed with EtOAc. The filtrate was concentrated under reduced pressure, the residue was partitioned between EtOAc and NH₄Cl solution, the organic layer was washed with NH₄Cl, Na₂CO₃ soln.
 10 brine, dried over Na₂SO₄ and purified by silica column chromatography (10% to 35% EtOAc/Hex) to afford 3-bromo-1-cyclopropyl-1H-pyrazole .
 3-bromo-1-cyclopropyl-1H-pyrazole (1.5 g, 8.18 mmol) was combined with 3,5-Difluoro-4-formylphenylboronic acid (1.8 g, 9.8 mmol), PdCl₂(tBu₂PPh)₂ (0.29 g, 0.41 mmol), and potassium phosphate tribasic monohydrate (4.71 g, 20.45 mmol) in 2-methyltetrahydrofuran (60
 15 mL) and water (60 mL) was degassed for 10 min with argon, then heated to reflux for 3 h. The reaction mixture was cooled to room temperature, the organic layer was separated and the aqueous layer was extracted into EtOAc. The combined organic layers were washed with 1M HCl, then brine, filtered and concentrated under reduce pressure, the residue was diluted with EtOAc and washed with brine 2x then dried over Na₂SO₄, filtered and concentrated under
 20 reduced pressure. This mixture was purified by silica column chromatography (50% to 100% DCM/Hex-10% EtOAc/DCM) to afford **P13** (1.2 g, 49%) MS (ESI) m/z 249.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 10.33 (s, 1H), 7.52 (d, J = 2.4 Hz, 1H), 7.42 (d, J = 10.1 Hz, 2H), 6.57 (d, J = 2.4 Hz, 1H), 3.66 (tt, J = 7.4, 3.9 Hz, 1H), 1.26 - 1.15 (m, 2H), 1.09 (qd, J = 5.7, 2.4 Hz, 2H).

25

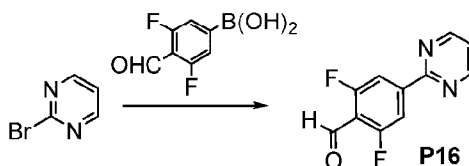


Synthesis of 2,6-difluoro-4-(4-fluoropyridin-2-yl)benzaldehyde (P14). A suspension of 2-bromo-5-fluoropyridine (0.95 g, 5.39 mmol), 3,5-Difluoro-4-formylphenylboronic acid (0.8 g, 4.3 mmol), bis(triphenylphosphine) palladium (II) dichloride (302 mg, 0.43 mmol), and
 30 potassium carbonate (1.49 g, 10.76 mmol) in a mixture of DME (10 ml) and water (5 ml) was degassed for 10 min with argon, then heated at 85 °C overnight. The reaction mixture was

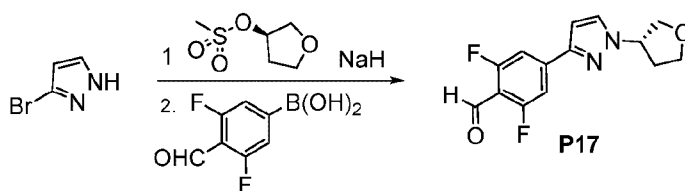
cooled to room temperature, concentrated under reduce pressure, the residue was diluted with EtOAc and washed with brine 2x then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (10% to 20% EtOAc/Hex) to afford **P14** (122 mg, 12%). MS (ESI) m/z 238.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 10.38 (d, J = 1.2 Hz, 1H), 8.59 (d, J = 2.8 Hz, 1H), 7.78 (ddd, J = 8.8, 4.2, 0.6 Hz, 1H), 7.68 - 7.60 (m, 2H), 7.55 (ddd, J = 8.8, 7.8, 2.9 Hz, 1H).



Synthesis of 2,6-difluoro-4-(4-fluoropyridin-2-yl)benzaldehyde (P15). The title compound **P15** was prepared according to the method presented for the synthesis of compound **P14** but instead utilizing 2-bromo-4-fluoropyridine. MS (ESI) m/z 238.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 10.39 (s, 1H), 8.70 (dd, J = 8.6, 5.5 Hz, 1H), 7.67 (d, J = 9.9 Hz, 3H), 7.48 (dd, J = 9.8, 2.3 Hz, 1H), 7.11 (ddd, J = 7.9, 5.5, 2.3 Hz, 1H).

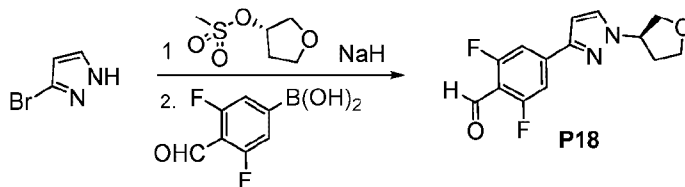


Synthesis of 2,6-difluoro-4-(pyrimidin-2-yl)benzaldehyde (P16). 2-bromopyrimidine (1g, 6.29 mmol) and tetrakis(triphenylphosphine)palladium (218.05 mg, 0.19 mmol) in 1,2-dimethoxyethane (30 ml) were degassed for 5 min, then Water (15 ml) was added followed by 3,5-difluoro-4-formylphenylboronic acid (1.4 g, 7.55 mmol) and sodium bicarbonate (1.0M in THF, 1.59 g, 18.87 mmol). The reaction mixture was heated at 85 °C overnight. After cooling to room temperature, the mixture was diluted with EtOAc and washed with sat. NaHCO₃ solution and brine then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0% to 40% EtOAc /Hex to afford **P16**. ¹H NMR (400 MHz, Chloroform-d) δ 10.42 (d, J = 1.0 Hz, 1H), 8.87 (d, J = 4.9 Hz, 2H), 8.16 - 8.03 (m, 2H), 7.32 (t, J = 4.8 Hz, 1H).

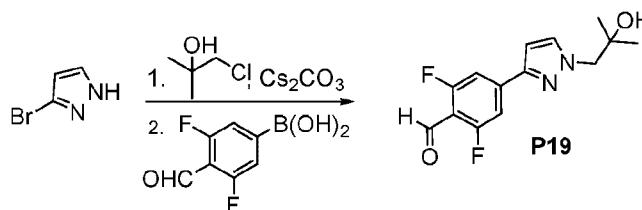


- (S)-2,6-difluoro-4-(1-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)benzaldehyde (P17)** To a solution of 3-bromo-1H-pyrazole (583 mg, 3.97 mmol) in DMF (15 mL) cooled in an ice bath was added sodium hydride (60% oil dispersion, 241 mg, 6.03 mmol). After stirring for 1.5 h, a solution of (R)-tetrahydrofuran-3-yl methanesulfonate (Reference: PCT Int Appl 2013068458) (998 mg, 6.01 mmol) in DMF (5mL) was added and the reaction mixture was heated to 100°C overnight. The reaction mixture was cooled to room temperature, diluted with EtOAc and washed with brine. The organic layer was separated, dried over Na₂SO₄, concentrated under vacuum and the crude residue was purified by silica column chromatography (20% to 40% EtOAc /Hex to afford (S)-3-bromo-1-(tetrahydrofuran-3-yl)-1H-pyrazole (0.17 g, 0.78 mmol), this material was combined in a 20 mL microwave vial with 3,5-Difluoro-4-formylphenylboronic acid (0.19 g, 1 mmol), palladium acetate (6.5 mg, 0.03 mmol), butyldi-1-adamantylphosphine (21.4 mg, 0.06 mmol), and potassium carbonate (0.33 g, 2.4 mmol) in a mixture of water (2 ml) and 1,4-dioxane (6 ml), the mixture was degassed with argon for 5 min. The reaction was microwaved at 100°C for 1.5 h, then cooled to room temperature, concentrated under vacuum, then diluted with EtOAc and washed with water and brine. The organic extract was dried over Na₂SO₄, filtered and concentrated under reduced pressure. This mixture was purified by silica column chromatography (20% to 40% EtOAc/hex) to afford **P17**. MS (ESI) m/z 279.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 10.32 (d, J = 1.0 Hz, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.48 - 7.34 (m, 2H), 6.62 (d, J = 2.4 Hz, 1H), 5.03 (ddt, J = 8.2, 5.8, 3.4 Hz, 1H), 4.31 - 4.03 (m, 4H), 3.98 (td, J = 8.6, 5.5 Hz, 1H), 2.51 (dtd, J = 13.4, 8.3, 7.1 Hz, 1H), 2.43 - 2.28 (m, 1H).

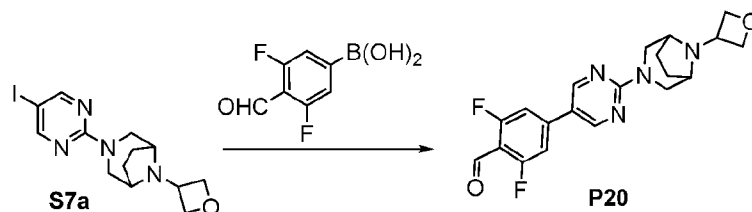
25



(R)-2,6-difluoro-4-(1-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)benzaldehyde (P18). The title compound **P18** was prepared according to the method presented for the synthesis of compound **P17** but instead utilizing (S)-tetrahydrofuran-3-yl methanesulfonate (Reference: PCT Int Appl 2013068458). MS (ESI) m/z 279.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 10.34 (d, J = 1.1 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.50 - 7.33 (m, 2H), 6.63 (d, J = 2.4 Hz, 1H), 5.04 (ddt, J = 9.0, 6.6, 3.5 Hz, 1H), 4.27 - 4.04 (m, 4H), 3.99 (td, J = 8.6, 5.5 Hz, 1H), 2.52 (dtd, J = 13.3, 8.2, 7.1 Hz, 1H), 2.38 (dddd, J = 13.3, 8.0, 5.5, 3.4 Hz, 1H).

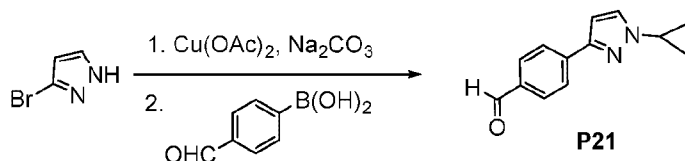


2,6-difluoro-4-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-3-yl)benzaldehyde (P19) The title compound **P19** was prepared according to the method presented for the synthesis of compound **P4** but instead utilizing 1-chloro-2-methylpropan-2-ol. MS (ESI) m/z 281.0 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 10.33 (s, 1H), 7.52 (d, J = 2.3 Hz, 1H), 7.47 - 7.35 (m, 2H), 6.64 (d, J = 2.4 Hz, 1H), 4.13 (s, 2H), 1.22 (s, 7H).



Synthesis of 2,6-difluoro-4-(2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)benzaldehyde (P20). A suspension of **S7a** (0.14 g, 3.7 mol), (3,5-difluoro-4-formylphenyl)boronic acid (110.29 mg, 5.9 mol), potassium carbonate (0.15 g, 1 mmol), and tetrakis(triphenylphosphine)palladium (20 mg, 0.19 mmol) in a mixture of dioxane (15 ml) and water (15 ml) was degassed for 10 min. The reaction mixture was heated at 85 °C for 3 h. After cooling to room temperature, the mixture was diluted with EtOAc and washed with sat. $NaHCO_3$ solution and brine then dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0% to 40% EtOAc /Hex to afford **P20** (99 mg, 62%). MS (ESI) m/z 387.2 $[M+H]^+$. 1H NMR (400 MHz,

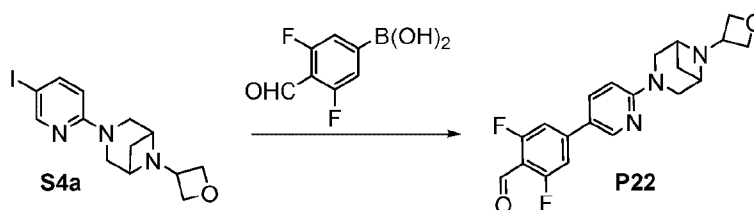
Chloroform-d) δ 10.33 (s, 1H), 8.55 (s, 1H), 7.11 (d, J = 9.8 Hz, 1H), 4.74 (t, J = 6.3 Hz, 1H), 4.61 (s, 1H), 4.40 (d, J = 12.8 Hz, 1H), 3.69 (s, 1H), 3.33 - 3.02 (m, 3H), 1.86 (s, 1H), 1.65 (d, J = 8.1 Hz, 1H), 1.55 (s, 2H).



5

Synthesis of 4-(1-cyclopropyl-1H-pyrazol-3-yl)benzaldehyde (P21). The title compound **P21** was prepared according to the method presented for the synthesis of compound **P13** but instead utilizing (4-formylphenyl)boronic acid. MS (ESI) m/z 213.2 $[M+H]^+$. 1H NMR (400 MHz, Chloroform-d) δ 10.01 (s, 1H), 7.97 (d, J = 8.3 Hz, 2H), 7.92 - 7.86 (m, 2H), 7.50 (d, J = 2.3 Hz, 1H), 6.61 (d, J = 2.3 Hz, 1H), 3.66 (tt, J = 7.4, 3.8 Hz, 1H), 1.22 - 1.15 (m, 2H), 1.11 - 1.03 (m, 2H).

10

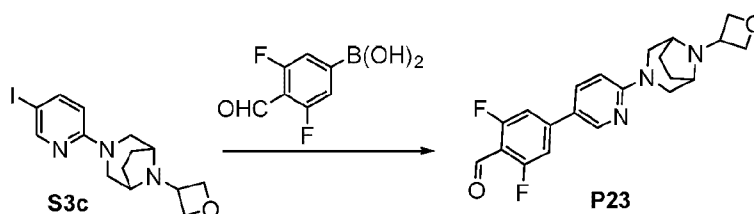


Synthesis of 2,6-difluoro-4-(6-(6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)benzaldehyde (P22) A suspension of **S4a** (0.53 g, 1 mmol), by (3,5-difluoro-4-formylphenyl)boronic acid (413.8 mg, 2.0 mmol), and potassium carbonate (0.16 g, 4 mmol), and $Cl_2Pd(tBu_2PPh)_2$ (0.02 g, 0.37 mmol) in a mixture of dioxane (15 ml) and water (15 ml) were degassed for 10 min.. The reaction mixture was heated at 60 °C for 3 h. After cooling to room temperature, the mixture was diluted with EtOAc and washed with sat. $NaHCO_3$ solution and brine then dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (1% to 15% (MeOH/ (1% E_3N in EtOAc) to afford **P22** (470 mg, 85%). MS (ESI) m/z 372.2 $[M+H]^+$. 1H NMR (400 MHz, Chloroform-d) δ 10.34 (s, 1H), 8.52 (d, J = 2.5 Hz, 1H), 7.76 (dd, J = 8.9, 2.5 Hz, 1H), 7.16 (d, J = 10.4 Hz, 2H), 6.61 (d, J = 8.8 Hz, 1H), 4.71 (t, J = 6.2 Hz, 2H), 4.50 (s, 2H), 3.87 (t, J = 6.2 Hz, 3H), 3.57 (s, 4H), 2.78 (d, J = 7.3 Hz, 1H), 1.64 (d, J = 8.9 Hz, 1H).

15

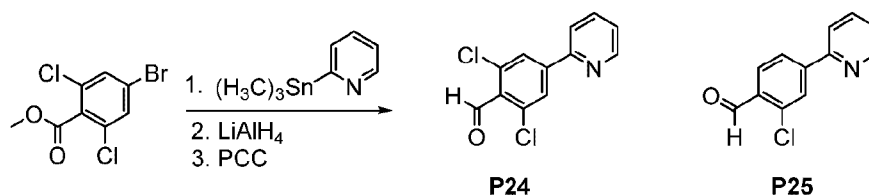
20

25



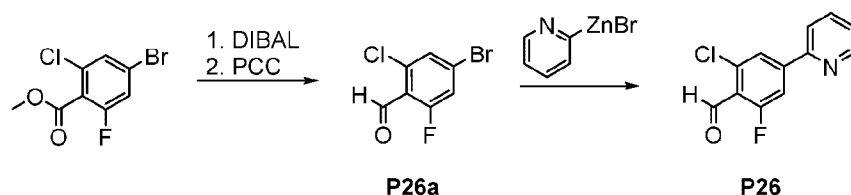
Synthesis of 2,6-difluoro-4-(6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)benzaldehyde (P23) The title compound **P23** was prepared according to the method

- 5 presented for the synthesis of compound **P20** but instead utilizing **S3c**. MS (ESI) m/z 386.1 $[\text{M}+\text{H}]^+$.



- Synthesis of 2,6-dichloro-4-(pyridin-2-yl)benzaldehyde (P24) and 2-chloro-4-(pyridin-2-yl)benzaldehyde (P25).** In a sealed tube, methyl 4-bromo-2,6-dichlorobenzoate both (3.18 g, 11.2 mmol) and 2-(trimethylstannyl)pyridine (1.94 ml, 11.2 mmol) and tetrakis(triphenyl phosphine)palladium (647.1 mg, 0.56 mmol) are suspended in DMF (25 mL). The mixture was degassed with argon for 10 min heated to 100 °C for 18 hours, and then at room temperature. After 48 h the reaction was diluted with EtOAc and washed with KF (3 g in 50 mL water) and brine (3x) and dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0% to 20% EtOAc/ hexanes) to afford methyl 2,6-dichloro-4-(pyridin-2-yl)benzoate (1.5 g, 47.5%). This material was dissolved in THF (25mL), cooled to 0 °C, then lithium aluminum hydride (0.4 g, 10.63 mmol) was added slowly, after the addition was completed, the reaction mixture was warmed up slowly to room temperature and stirred for 1 h, then cooled back to 0 °C added water (500 uL) slowly (vigorous gas evolution), followed by NaOH (2 M, 500 uL) then water (1500 uL). The slurry was stirred at room temperature. After 1 h, Na_2SO_4 was added, and then the mixture was filtered through Celite. The solid was rinsed with Et_2O (~200 mL), and the filtrate was concentrated under reduced pressure, the residue was diluted with EtOAc and washed with water then dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue (1.5 g, 5.9 mmol) was combined with pyridinium chlorochromate (1.91 g, 8.85 mmol) and Celite (700 mg, 7

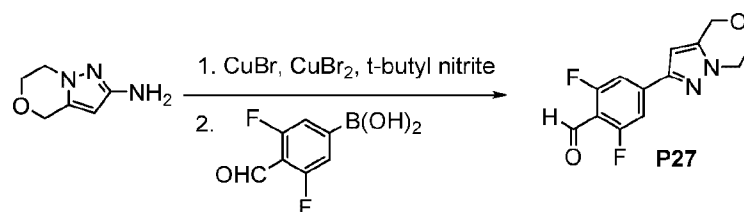
mmol), DCM (10 mL) was added and the reaction mixture was stirred at room temperature for 48 h. The reaction was filtered through a Celite frit with a small plug of silica, and rinsed several times with DCM/EtOAc, and then the filtrate was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography to afford **P24** (392 mg, 26.3%). MS (ESI) *m/z* 252.0 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 10.54 (s, 1H), 8.74 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.06 (s, 2H), 7.83 (ddd, *J* = 8.0, 7.4, 1.8 Hz, 1H), 7.77 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.36 (ddd, *J* = 7.4, 4.8, 1.2 Hz, 1H) and **P25** (195 mg, 15.2%). MS (ESI) *m/z* 218.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 10.52 (d, *J* = 0.8 Hz, 1H), 8.74 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 8.17 (dd, *J* = 1.6, 0.5 Hz, 1H), 8.07 - 7.95 (m, 2H), 7.91 - 7.75 (m, 2H), 7.39 - 7.29 (m, 1H).



Synthesis 4-bromo-2,6-difluorobenzaldehyde (P26a) To a solution of methyl 4-bromo-2-chloro-6-fluorobenzoate (5.6 g, 20.94 mmol) in DCM (100 mL) at -78°C, was added dropwise diisobutylaluminum hydride (1.0M in toluene, 60 ml). After 4.5 h the reaction mixture was quenched with MeOH (2.4 mL), then NaOH (6.0 M, 2.4 mL) followed by water (5 mL). The reaction was stirred for 1 h, and then Na₂SO₄ was added, filtered, and concentrated under vacuum, the residue (4.96 g, 20.71 mmol) was dissolved in DCM (100 mL) and cooled to 5°C, then pyridinium chlorochromate (6.27 g, 0.03 mol) was added and the mixture was stirred overnight, allowing to slowly warm to room temperature. Silica gel (10 g) was added, the mixture was filtered through a 1.5 inch plug of silica gel eluting with 5:1 DCM/EtOAc to give **P26a** (4.67 g, 92%). ¹H NMR (400 MHz, Chloroform-d) δ 10.38 (s, 1H), 7.54 - 7.41 (m, 1H), 7.31 (dd, *J* = 9.7, 1.8 Hz, 1H). ¹⁹F NMR (377 MHz, Chloroform-d) δ -113.31 (d, *J* = 9.7 Hz).

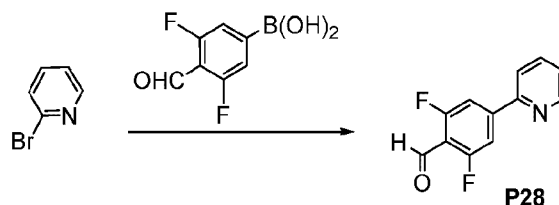
Synthesis of 2-chloro-6-fluoro-4-(pyridin-2-yl)benzaldehyde (P26) To a solution of **P26a** (2.5 g, 10.53 mmol) and Pd(tBu₂PPh)₂Cl₂ (213 mg, 0.34 mmol) in methyl tetrahydrofuran (7 mL) at room temperature, was added 2-pyridylzinc bromide (0.5M in THF, 28.43 ml). The reaction was degassed with Ar for 10 min, and then warmed to 60°C. After 3h the mixture was cooled to room temperature, diluted with EtOAc and washed with saturated solution of NH₄Cl. The organic extract was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (3% - 35% EtOAc in 1:1

DCM/hexane) to afford **P26** (1.09 g, 41%) MS (ESI) m/z 236.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 10.49 (d, J = 1.1 Hz, 1H), 8.74 (ddd, J = 4.8, 1.8, 1.0 Hz, 1H), 7.96 (t, J = 1.4 Hz, 1H), 7.86 (d, J = 1.8 Hz, 0H), 7.85 - 7.80 (m, 1H), 7.78 (q, J = 1.1 Hz, 1H), 7.77 - 7.74 (m, 1H), 7.36 (ddd, J = 7.4, 4.8, 1.2 Hz, 1H). ^{19}F NMR (377 MHz, Chloroform- d) δ -114.35 (d, J = 11.6 Hz).

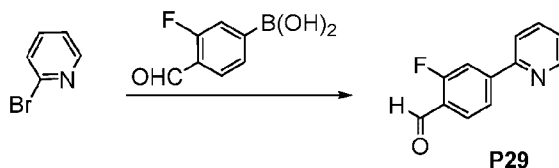


Synthesis of 4-(6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-yl)-2,6-difluorobenzaldehyde

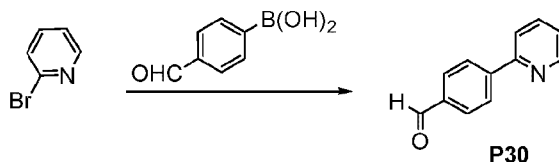
(P27). 6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-amine (1 g, 0.01 mol) in CH_3CN (5 mL) at 15°C was combined with cuprous bromide (1.24 g, 0.01 mol) and Cupric bromide (16.05 mg, 0.07 mmol), then tert-Butyl nitrite (1.11 mL, 0.01 mol) was added very slowly and the reaction was stirred overnight. The mixture was quenched with aqueous NH_4Cl , diluted with DCM, the layers were splitted, and the organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (7%-40% EtOAc/ hexanes), the product (0.59 g, 2.91 mmol) was combined with 3,5-Difluoro-4-formylphenylboronic acid (0.81 g, 4.36 mmol), $PdCl_2(tBu_2PPh)_2$ (0.08 g, 0.12 mmol), and potassium phosphate tribasic monohydrate (1.67 g, 7.27 mmol) in 2-methyltetrahydrofuran (25 mL) and water (60 mL) was degassed for 10 min with argon, then heated to reflux for 3 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with water, 5% citric acid solution, and brine. The separated organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was crystallized from EtOAc/ether to afford **P27** (486 mg, 63%) MS (ESI) m/z 265.1 $[M+H]^+$.



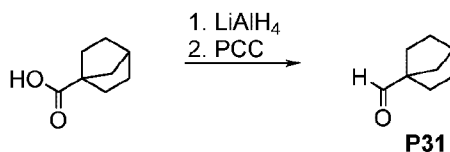
Synthesis of 2,6-difluoro-4-(pyridin-2-yl)benzaldehyde (P28). The title compound **P28** was prepared according to the method presented for the synthesis of compound **P20** but instead utilizing 2-bromopyridine. MS (ESI) m/z 202.2 $[M+H]^+$.



Synthesis of 2,6-difluoro-4-(pyridin-2-yl)benzaldehyde (P29). The title compound **P29** was prepared according to the method presented for the synthesis of compound **P20** but instead utilizing 2-bromopyridine and (3-fluoro-4-formylphenyl)boronic acid. MS (ESI) m/z 220.2 $[M+H]^+$.

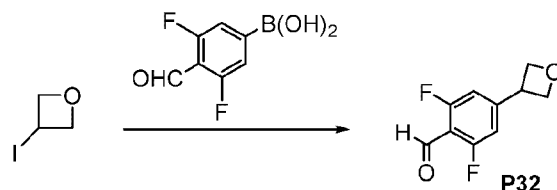


Synthesis of 4-(pyridin-2-yl)benzaldehyde (P30). The title compound **P30** was prepared according to the method presented for the synthesis of compound **P20** but instead utilizing 2-bromopyridine and (4-formylphenyl)boronic acid. MS (ESI) m/z 184.1 $[M+H]^+$.

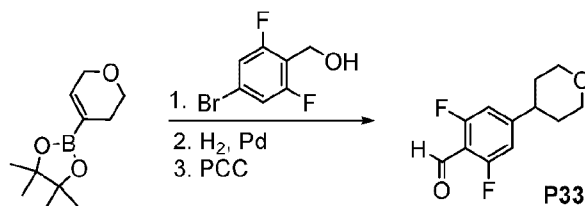


Synthesis of bicyclo[2.2.1]heptane-1-carbaldehyde (P31) Bicyclo[2.2.1]heptane-1-carboxylic acid (1000 mg, 0.01 mol) was dissolved in methyl tetrahydrofuran (3 mL), cooled to 0°C , then lithium aluminum hydride (0.5 g, 14 mmol) was added slowly, after the addition was completed, the reaction mixture was warmed up slowly to room temperature and stirred for 2 h, the mixture was cooled back to 0°C added water (540 μL) slowly (vigorous gas evolution), followed by NaOH (2 M, 540 μL) then water (1500 μL). The slurry was stirred at room temperature. After 1 h Na_2SO_4 was added then the mixture was filtered through Celite. The solid was rinsed with DCM (~ 200 mL), and the filtrate was concentrated under reduced pressure. The crude residue (900 mg, 7.13 mmol) was dissolved in DCM (10 mL) cooled in an ice bath and combined with

pyridinium chlorochromate (2.61 g, 12.12 mmol) and Celite (700 mg, 7 mmol), the reaction was allowed to war up to room temperature slowly and stirred for 48 h. The reaction was filtered through a Celite frit with a small plug of silica, and rinsed several times with DCM, and then the filtrate was concentrated under reduced pressure at 5°C to afford **P31** (1.7 g, 95%). ¹H NMR (400 MHz, Chloroform-d) δ 9.85 (s, 1H), 2.41 (td, J = 4.2, 2.1 Hz, 1H), 2.04 - 1.27 (m, 10H).



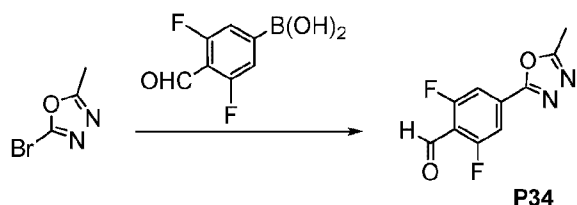
Synthesis of 2,6-difluoro-4-(oxetan-3-yl)benzaldehyde (P32) In a sealed tube, 3-Iodo-oxetane (0.24 ml, 3 mmol), (3,5-difluoro-4-formylphenyl)boronic acid (250 mg, 1.34 mmol), 4,4'-Di-tert-butyl-2,2'-dipyridyl (18.05 mg, 0.07 mmol) Ni(NO₃)₂ · 6H₂O (19.55 mg, 0.07 mmol) and Potassium carbonate (557.51 mg, 4.03 mmol) in 1,4-Dioxane (5 ml) were combined. The mixture was degased with argon for 10 min heated to 80°C for 12 hours, and then cooled to room temperature. After 48 h the reaction was diluted with EtOAc and washed with brine (2x) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (10% to 30% EtOAc/ hexanes) to afford P32 (49 mg, 18 %). ¹H NMR (400 MHz, Chloroform-d) δ 10.26 (d, J = 1.2 Hz, 1H), 6.99 (d, J = 9.5 Hz, 2H), 5.04 (dd, J = 8.2, 6.3 Hz, 2H), 4.62 (t, J = 6.3 Hz, 2H), 4.14 (tt, J = 8.2, 6.2 Hz, 1H).



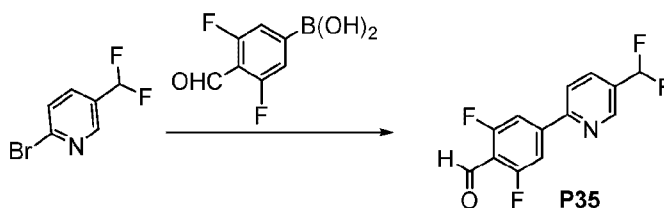
Synthesis of 2,6-difluoro-4-(tetrahydro-2H-pyran-4-yl)benzaldehyde (P33) 3,6-Dihydro-2H-pyran-4-boronic acid pinacol ester (414.48 mg, 1.97 mmol), 4-Bromo-2,6-difluorobenzyl alcohol (0.4 g, 2 mmol), tetrakis(triphenylphosphine)palladium (103.63 mg, 0.09 mmol), and sodium carbonate (2M, 2.24 mL) in 1,4-dioxane (6 ml) were combined. The mixture was degased with argon for 10 min heated to 80°C for 12 hours, and then cooled to room temperature. The reaction was diluted with EtOAc and washed with brine (2x) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by

silica column chromatography (20% to 50% EtOAc/ hexanes), the product (405 mg, 1.79 mmol) was dissolved in EtOAc (8 mL), Palladium (10% on C, 38.1 mg, 0.36 mmol) was added and the mixture was stirred at room temperature under hydrogen for 18 h. The mixture was filtered through Celite, and rinsed several times with EtOAc, the filtrate was concentrated under reduced pressure.

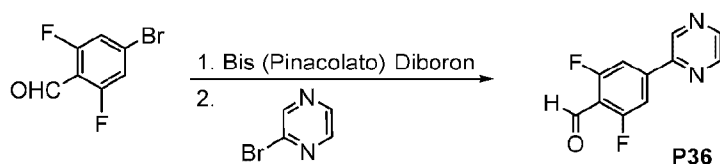
The crude residue (450 mg, 1.97 mmol) was dissolved in DCM (10 mL) and combined with pyridinium chlorochromate (637.49 mg, 2.96 mmol), the reaction was stirred at room temperature for 48 h. The reaction was then filtered through a Celite and rinsed several times with DCM, the filtrate was concentrated under reduced pressure to afford **P33**. ¹H NMR (400 MHz, Chloroform-d) δ 10.28 (d, J = 1.2 Hz, 1H), 6.85 (d, J = 10.0 Hz, 2H), 4.08 (dt, J = 11.5, 3.2 Hz, 2H), 3.60 – 3.33 (m, 2H), 2.90 – 2.71 (m, 1H), 1.83 – 1.70 (m, 4H).



Synthesis of 2,6-difluoro-4-(5-methyl-1,3,4-oxadiazol-2-yl)benzaldehyde (P34). The title compound **P34** was prepared according to the method presented for the synthesis of compound **P1** but instead utilizing 2-bromo-5-methyl-1,3,4-oxadiazole. MS (ESI) m/z 225.1[M+H]⁺.

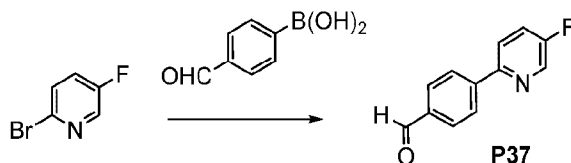


Synthesis of 4-(5-(difluoromethyl)pyridin-2-yl)-2,6-difluorobenzaldehyde (P35). The title compound **P35** was prepared according to the method presented for the synthesis of compound **P1** but instead utilizing 2-bromo-5-(difluoromethyl)pyridine. MS (ESI) m/z 270.1[M+H]⁺.

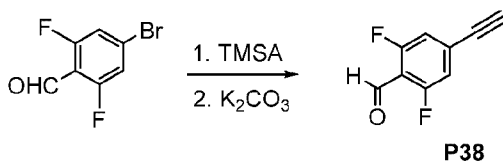


Synthesis of 2,6-difluoro-4-(pyrazin-2-yl)benzaldehyde (P36). A mixture of 4-bromo-2,6-difluorobenzaldehyde (2 g, 9.05 mmol), bis (pinacolato) diboron (3.22 g, 12.67 mmol), dichloro

1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (739.04 mg, 0.9 mmol) and potassium acetate (1776.34 mg, 18.1 mmol) in 1, 4-dioxane (18 mL) were heated to 90°C for 12 hours. After cooling to room temperature 2-bromopyrazine (1.64 ml, 18.1 mmol), tetrakis(triphenylphosphine)palladium (1.05g, 0.9 mmol) and potassium carbonate (2 M, 11.31 ml) were added. The mixture was degassed by pulling vacuum and back-filling with Ar (3x), then the reaction was heated to 90°C for 12 hours, cooled to room temperature, diluted with EtOAc and washed with saturated solution of brine. The organic extract was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0% - 100% EtOAc /DCM/) to afford **P36** MS (ESI) m/z 221.1 [M+H]⁺.



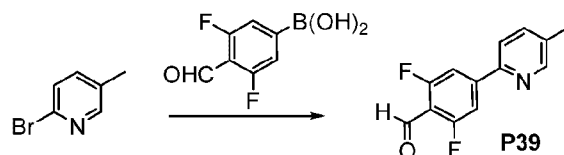
Synthesis of 4-(5-fluoropyridin-2-yl)benzaldehyde (P37). The title compound **P37** was prepared according to the method presented for the synthesis of compound **P14** of but instead utilizing (4-formylphenyl)boronic acid. MS (ESI) m/z 202.14 [M+H]⁺.



Synthesis of 4-ethynyl-2,6-difluorobenzaldehyde (P38). A solution of 4-bromo-2,6-difluorobenzaldehyde Reactant 2 (6 g, 27.15 mmol), CuI (517.06 mg, 2.71 mmol) PdCl₂(tBu₂PPh)₂ (955.53 mg, 1.36 mmol) trimethylsilylacetylene (7.67 ml, 54.3 mmol) in a 3:1 mixture of CH₃CN (50 mL)/ Et₃N (10 mL) was degassed with Argon for 10 min. The reaction mixture was heated to 70 °C for 18 h. After cooling to room temperature the mixture was filtered through silica, the filtrate was concentrated and purified by silica column chromatography (1% - 15% EtOAc /Hex) The product was dissolved in MeOH (5 ml) and Potassium carbonate (1876.01 mg, 13.57 mmol) were added, the mixture was stirred at room temperature. After 20

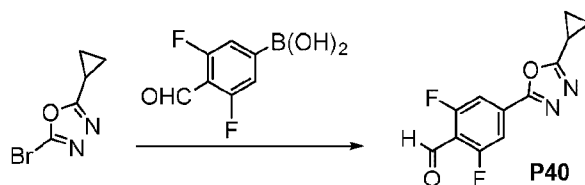
min the reaction was concentrated to dryness, then diluted with DCM and washed with brine. The organic extract was dried over Na₂SO₄ to give **P38** (2.99 g, 66%). ¹H NMR (400 MHz, Chloroform-d) δ 10.30 (d, J = 1.1 Hz, 1H), 7.04 (d, J = 9.1 Hz, 2H), 0.26 (s, 9H).

5



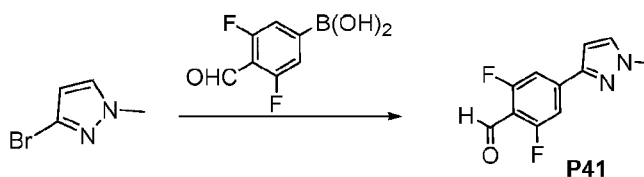
Synthesis of 2,6-difluoro-4-(5-methylpyridin-2-yl)benzaldehyde (P39). The title compound **P39** was prepared according to the method presented for the synthesis of compound **P16** but instead utilizing 2-bromo-5-methylpyridine.

10



Synthesis of 4-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-2,6-difluorobenzaldehyde (P40). The title compound **P40** was prepared according to the method presented for the synthesis of compound **P1** but instead utilizing 2-bromo-5-cyclopropyl-1,3,4-oxadiazole. MS (ESI) m/z 251.1 [M+H]⁺.

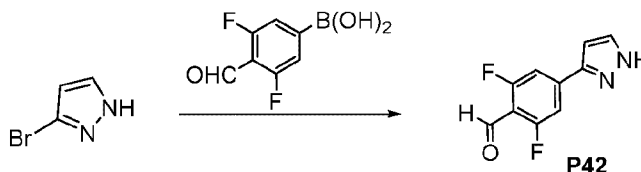
15



Synthesis of 2,6-difluoro-4-(1-methyl-1H-pyrazol-3-yl)benzaldehyde (P41) A solution of 3-bromo-1-methyl-1H-pyrazole (0.14 g, 3.7 mmol), (3,5-difluoro-4-formylphenyl)boronic acid (9.19 g, 49.43 mmol), sodium carbonate (8.72 g, 82.27 mmol), and tetrakis(triphenylphosphine)palladium (1.9 g, 1.64 mmol) in a mixture of 1,2-Dimethoxyethane (84 ml) and water (36 ml) was degassed for 10 min. The reaction mixture was heated at 100 °C for 18 h. After cooling to room temperature, the mixture was diluted concentrated in vacuo then diluted with EtOAc and washed with brine then dried over Na₂SO₄, filtered and concentrated

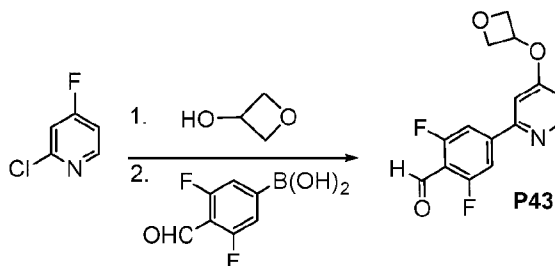
20

under reduced pressure. The crude residue was purified by silica column chromatography (20% to 40% EtOAc /Hex to afford **P41**. MS (ESI) m/z 223.3 $[M+H]^+$.



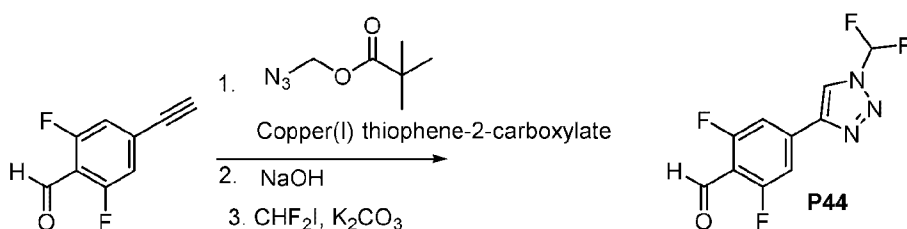
Synthesis of 2,6-difluoro-4-(1H-pyrazol-3-yl)benzaldehyde (P42). The title compound **P42**

- 5 was prepared according to the method presented for the synthesis of compound **P1** but instead utilizing 3-bromo-1H-pyrazole. MS (ESI) m/z 209.1 $[M+H]^+$.

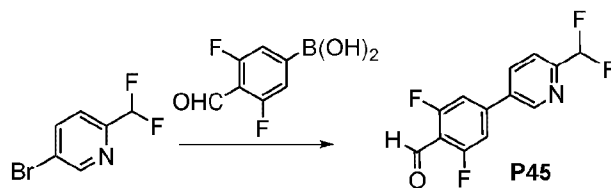


Synthesis of 2,6-difluoro-4-(4-(oxetan-3-yloxy)pyridin-2-yl)benzaldehyde (P43). To a

- 10 suspension of NaH (60%, 310.79 mg, 7.77 mmol) in THF (11 mL) was added oxetan-3-ol (0.42 mL, 6.66 mmol) dropwise, the mixture was stirred for 30 minutes followed by addition of 2-chloro-4-fluoropyridine (0.5 mL, 5.55 mmol). The reaction mixture was stirred overnight, diluted with EtOAc and washed with water and brine then dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (30% to 60% EtOAc /Hex) the product (849 mg, 4.57 mmol) was combined with (3,5-difluoro-4-
- 15 formylphenyl)boronic acid (1020.52 mg, 5.49 mmol) potassium carbonate (2M, 5.49 mL) and $Pd(dppf)Cl_2$ (279.29 mg, 0.46 mmol) in DME (23 mL), the mixture was degassed by pulling vacuum and back-filling with Ar (5x) heated to reflux for 3 h. After cooling to room temperature, the mixture was diluted with EtOAc and washed with water and brine then dried
- 20 over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (30% to 60% EtOAc /Hex) to afford **P43** (1.22 g, 80%). MS (ESI) m/z 292.1 $[M+H]^+$.

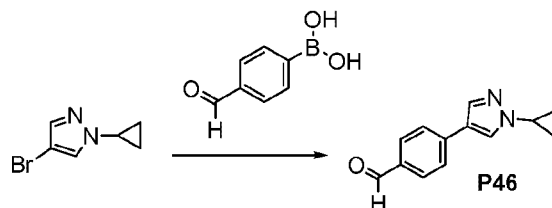


Synthesis of 4-(1-(difluoromethyl)-1H-1,2,3-triazol-4-yl)-2,6-difluorobenzaldehyde (P44). 4-ethynyl-2,6-difluorobenzaldehyde (1.5 g, 9.0 mmol) was dissolved in THF (10 mL). Copper(I) thiophene-2-carboxylate (115.71 mg, 0.9 mmol) was added followed by azidomethyl pivalate (2.1 mL, 13.5 mmol) over 5 minutes. After 15 minutes, complete conversion was observed by LCMS analysis. The reaction was quenched with aqueous NaHCO_3 , and the intermediate product was extracted into ethyl acetate, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was slurried in 40 mL 1:1 MeOH:EtOH, and aqueous NaOH solution was added (2M, 9.9 mL, 19.9 mmol). After 30 minutes aqueous NaHCO_3 was added, and the intermediate product was extracted into ethyl acetate, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was transferred using THF (20 mL) to a 500 mL pressure vessel containing potassium carbonate (4.4 g, 32 mmol) and a magnetic stir bar. A solution of difluoroiodomethane (10% in THF, 68 mL, 36 mmol) was added and the vessel was sealed. The mixture was stirred overnight at 50 °C overnight. The crude mixture was filtered, concentrated *in vacuo* and purified by flash column chromatography (0 → 25% EtOAc in 1:1 hexanes:DCM). The desired regioisomer was major and was isolated in the middle fractions. ^1H NMR (400 MHz, Chloroform- d) δ 10.36 (s, 1H), 8.31 (s, 1H), 7.62 (t, J = 58.8 Hz, 1H), 7.59 - 7.51 (m, 2H). ^{19}F NMR (377 MHz, Chloroform- d) δ -95.78 (d, J = 58.9 Hz), -113.68 (d, J = 9.2 Hz).

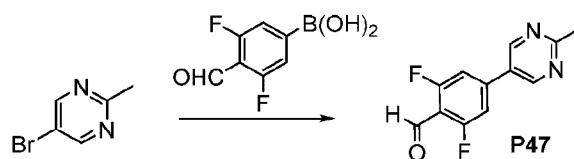


Synthesis of 4-(6-(difluoromethyl)pyridin-3-yl)-2,6-difluorobenzaldehyde (P45). The title compound **P45** was prepared according to the method presented for the synthesis of compound **P16** but instead utilizing 5-bromo-2-(difluoromethyl)pyridine. ^1H NMR (400 MHz, Chloroform- d) δ 10.40 (s, 1H), 8.94 - 8.79 (m, 1H), 8.04 (dd, J = 8.2, 2.3 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H),

7.25 (d, $J = 9.3$ Hz, 2H), 6.70 (t, $J = 55.2$ Hz, 1H). ^{19}F NMR (377 MHz, Chloroform- d) δ -113.37 (d, $J = 9.3$ Hz), -116.56 (d, $J = 55.5$ Hz).



- 5 **Synthesis of 4-(1-cyclopropyl-1H-pyrazol-4-yl)benzaldehyde (P46).** The title compound **P46** was prepared according to the method presented for the synthesis of compound **P7** but instead utilizing (4-formylphenyl)boronic acid and 4-bromo-1-cyclopropyl-1H-pyrazole. MS (ESI) m/z 213.2 $[\text{M}+\text{H}]^+$.

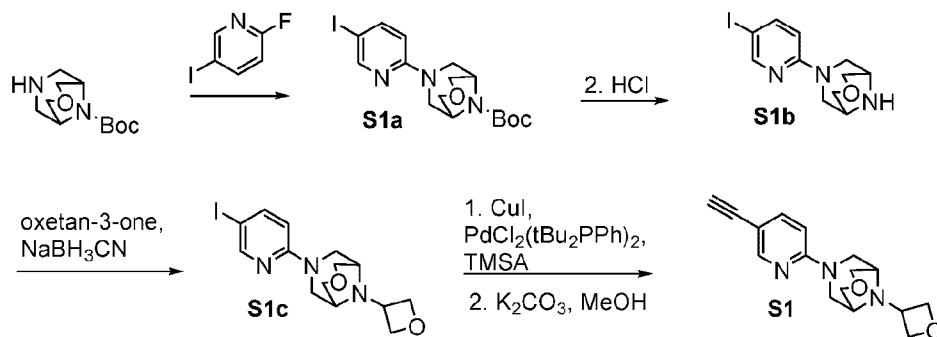


10

- Synthesis of 2,6-difluoro-4-(2-methylpyrimidin-5-yl)benzaldehyde (P47).** The title compound **P47** was prepared according to the method presented for the synthesis of compound **P16** but instead utilizing 5-bromo-2-methylpyrimidine. MS (ESI) m/z 235.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 10.38 (t, $J = 1.0$ Hz, 1H), 8.86 (s, 2H), 7.30 - 7.14 (m, 3H), 2.82 (s, 3H).

15

2.2 SYNTHESIS OF S INTERMEDIATES



20

Synthesis of *tert*-butyl 7-(5-iodopyridin-2-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate (S1a).

A solution of *tert*-butyl 3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate (1 g, 4.38 mmol) 2-fluoro-5-iodopyridine (1.12 g, 5.04 mmol), and sodium carbonate (0.84 g, 7.88 mmol) in 1-Methyl-2-pyrrolidinone (4 ml) was heated at 85 °C overnight. The mixture was cooled to room temperature, diluted with water and extracted into DCM. The organic extract was dried over Na₂SO₄ filtered and concentrated under reduced pressure. The residue was purified by silica chromatography to yield **S1a** (1.57 g, 62.3%). MS (ESI) *m/z* 431.9 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.30 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.66 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.44 (d, *J* = 9.0 Hz, 1H), 4.25 (d, *J* = 12.7 Hz, 1H), 4.21 - 4.00 (m, 3H), 3.97 - 3.86 (m, 2H), 3.80 (t, *J* = 11.9 Hz, 2H), 3.26 (t, *J* = 15.1 Hz, 2H), 1.48 (s, 9H).

Synthesis of 7-(5-iodopyridin-2-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane (S1b). To a solution of **S1a** (1.57 g, 0.004 mol) in DCM (15 mL) in a water bath at room temperature was added was added HCl (4.0M in dioxane, 4.6 mL). The reaction was stirred at room temperature overnight. The reaction was concentrated to dryness. MS (ESI) *m/z* 332.0 [M+H]⁺. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.26 (dd, *J* = 2.2, 0.7 Hz, 1H), 8.22 (ddd, *J* = 9.5, 2.2, 1.0 Hz, 1H), 7.27 (d, *J* = 9.7 Hz, 1H), 4.60 (d, *J* = 14.4 Hz, 2H), 4.21 (dt, *J* = 13.5, 0.9 Hz, 2H), 4.08 (dt, *J* = 13.3, 2.4 Hz, 2H), 3.88 (d, *J* = 14.6 Hz, 2H), 3.81 (s, 2H).

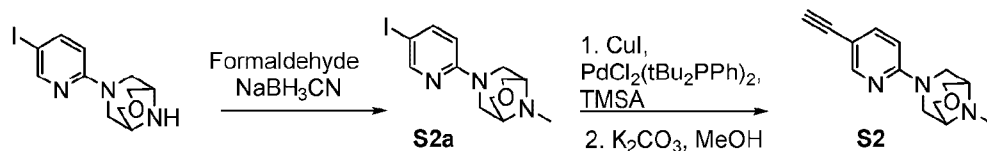
Synthesis of 7-(5-iodopyridin-2-yl)-9-(oxetan-3-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane

(S1c). To **S1b** (0.62 g, 8.62 mmol) suspended in NMP (6 mL), was added Et₃N (0.12 ml, 0.8 mmol), oxetan-3-one (0.51 ml, 8.5 mmol), and sodium cyanoborohydride (2.62 g, 41.72 mmol) was added and the reaction mixture was stirred for 5 min then more Et₃N (0.18 ml, 0.1 mmol), stirred at room temperature for 4 h, then warmed up to 30 °C. After 2 h the reaction was cooled to room temperature, diluted with EtOAc and washed with brine. The organic extract was dried over Na₂SO₄ filtered and concentrated under reduced pressure to afford **S1c** (0.84 g, 95%). MS (ESI) *m/z* 388.1 [M+H]⁺.

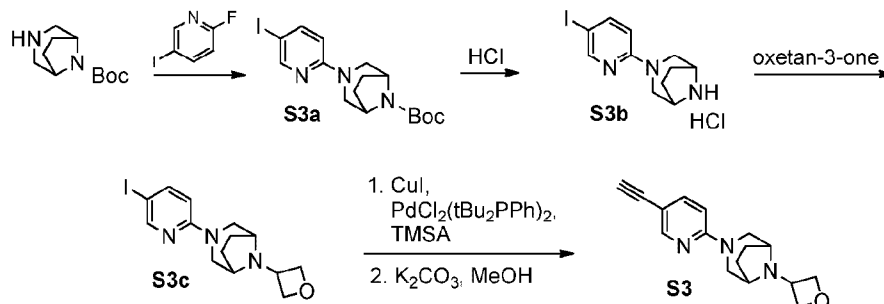
Synthesis of 7-(5-ethynylpyridin-2-yl)-9-(oxetan-3-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane

(S1) A solution of **S1c** (0.84 g, 0 mol), CuI (24.73 mg, 0.13 mmol) PdCl₂(tBu₂PPh)₂ (45.7 mg, 0.06 mmol), trimethylsilylacetylene (0.92 ml, 0.01 mol), in a 3:1 mixture of CH₃CN (9 mL)/ Et₃N (3 mL) was degassed with Argon for 10 min. The reaction mixture was heated to 40 °C for 90 min. The reaction was diluted with EtOAc and washed with NaHCO₃ solution and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was dissolved in MeOH (5 ml) and Potassium carbonate (0.45 g, 3.0 mmol) were added, the mixture was stirred at room temperature. After 15 min the reaction was concentrated to dryness, then diluted with DCM and washed with brine. The organic extract was dried over Na₂SO₄ to give **S1** (300

mg 48%). MS (ESI) m/z 286.2 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.17 (dd, J = 2.3, 0.8 Hz, 1H), 7.40 (dd, J = 8.9, 2.3 Hz, 1H), 6.35 (dd, J = 8.9, 0.8 Hz, 1H), 4.55 (t, J = 6.2 Hz, 2H), 4.42 (t, J = 5.9 Hz, 2H), 4.25 (p, J = 6.2 Hz, 1H), 3.84 (dt, J = 11.3, 2.2 Hz, 2H), 3.78 (d, J = 12.9 Hz, 2H), 3.71 (dt, J = 11.5, 0.9 Hz, 2H), 3.24 (ddd, J = 12.9, 4.9, 2.0 Hz, 2H), 2.92 (s, 1H), 2.65 - 2.52 (m, 2H).



Synthesis of 7-(5-ethynylpyridin-2-yl)-9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonane. The title compound **S2** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing formaldehyde. MS (ESI) m/z 244.2 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.33 (d, J = 2.3 Hz, 1H), 7.55 (dd, J = 8.9, 2.3 Hz, 1H), 6.52 (d, J = 8.9 Hz, 1H), 4.01 (d, J = 11.2 Hz, 2H), 3.91 (d, J = 12.9 Hz, 2H), 3.85 (d, J = 11.2 Hz, 2H), 3.53 (ddd, J = 13.0, 4.8, 2.0 Hz, 2H), 3.07 (s, 1H), 2.86 - 2.75 (m, 2H), 2.62 (s, 3H).



Synthesis of tert-butyl 3-(5-iodopyridin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (S3a) The title compound **S3a** was prepared according to the method presented for the synthesis of compound **S1a** but instead utilizing tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate. MS (ESI) m/z 415.8 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.36 - 8.26 (m, 1H), 7.65 (dd, J = 9.0, 2.4 Hz, 1H), 6.40 (d, J = 9.0 Hz, 1H), 4.33 (s, 2H), 3.82 (d, J = 40.5 Hz, 2H), 3.05 (s, 2H), 1.94 (dd, J = 8.7, 4.6 Hz, 2H), 1.73 (d, J = 7.3 Hz, 2H), 1.47 (s, 9H).

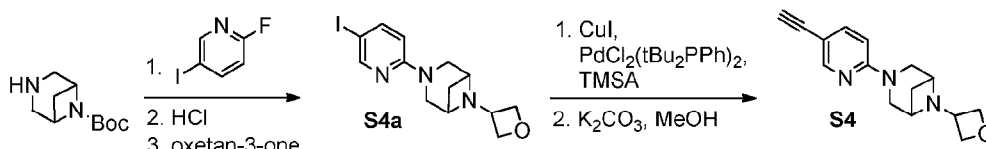
Synthesis of 3-(5-ethynylpyridin-2-yl)-3,8-diazabicyclo[3.2.1]octane hydrochloride (S3b) The title compound **S3b** was prepared according to the method presented for the synthesis of compound **S1b** but instead utilizing **S3a**. MS (ESI) m/z 316.1 $[M+H]^+$.

Synthesis of 3-(5-iodopyridin-2-yl)-8-(oxetan-3-yl)-3,8 diazabicyclo[3.2.1]octane (S3c)

The title compound **S3c** was prepared according to the method presented for the synthesis of compound **S1c** but instead utilizing **S3b**. MS (ESI) m/z 372.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.22 (d, J = 2.3 Hz, 1H), 7.57 (dd, J = 8.9, 2.4 Hz, 1H), 6.30 (d, J = 9.0 Hz, 1H), 4.65 (t, J = 6.3 Hz, 2H), 4.52 (t, J = 5.8 Hz, 2H), 3.70 (dd, J = 11.8, 2.4 Hz, 2H), 3.23 - 3.08 (m, 2H), 3.04 (dd, J = 11.7, 2.2 Hz, 2H), 1.87 - 1.70 (m, 2H), 1.63 (d, J = 7.5 Hz, 2H).

Synthesis of 3-(5-ethynylpyridin-2-yl)-8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octane (S3)

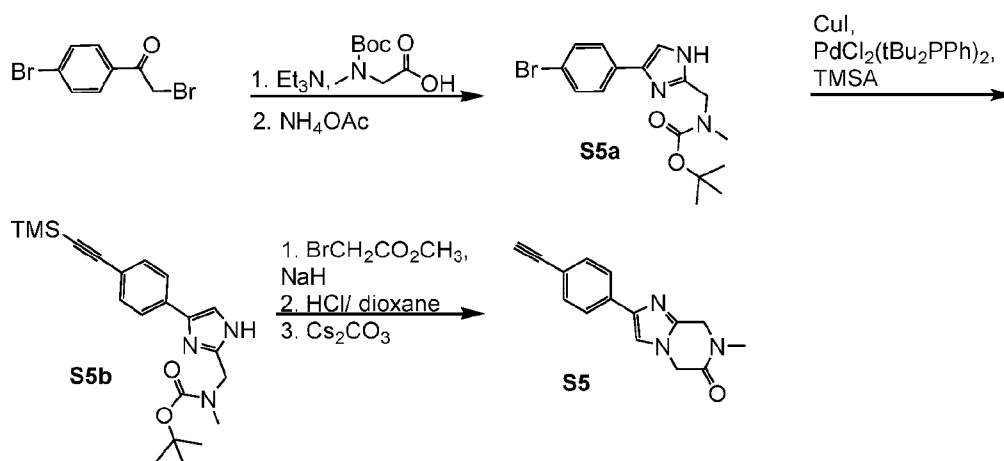
The title compound **S3** was prepared according to the method presented for the synthesis of compound **S1c** but instead utilizing **S3c**. MS (ESI) m/z 244.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.16 (d, J = 2.3 Hz, 1H), 7.55 (dd, J = 8.9, 2.3 Hz, 1H), 6.66 (d, J = 8.9 Hz, 1H), 4.76 (t, J = 6.4 Hz, 3H), 4.57 (t, J = 5.8 Hz, 3H), 3.88 (dd, J = 12.2, 2.4 Hz, 3H), 3.78 (ddd, J = 11.9, 6.5, 5.4 Hz, 1H), 3.43 (s, 1H), 3.29 (dd, J = 6.9, 1.7 Hz, 4H), 3.10 (dd, J = 11.9, 2.2 Hz, 3H), 1.93 (dd, J = 8.7, 4.4 Hz, 2H), 1.68 (t, J = 6.9 Hz, 2H).



Synthesis of 3-(5-iodopyridin-2-yl)-6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptane (S4a) The title compound **S4a** was prepared according to the method presented for the synthesis of compound **S1c** but instead utilizing *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate. MS (ESI) m/z 358.0 $[M+H]^+$.

Synthesis of 3-(5-ethynylpyridin-2-yl)-6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptane (S4).

The title compound **S4** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S4a**. MS (ESI) m/z 256.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.13 (d, J = 2.3 Hz, 1H), 7.53 (dd, J = 8.9, 2.3 Hz, 1H), 6.55 (d, J = 8.9 Hz, 1H), 4.65 (t, J = 6.3 Hz, 2H), 4.36 (dd, J = 6.3, 4.7 Hz, 2H), 3.77 (dd, J = 19.2, 5.7 Hz, 3H), 3.44 (s, 4H), 3.37 (s, 1H), 2.61 (dt, J = 9.1, 6.2 Hz, 1H), 1.54 (d, J = 9.1 Hz, 1H).



Synthesis of tert-butyl ((4-(4-bromophenyl)-1H-imidazol-2-yl)methyl)(methyl)carbamate (S5a)

To a solution of N-(tert-butoxycarbonyl)-N-methylglycine (4.81 g, 25.41 mmol) and 2,4'-dibromoacetophenone (6.42 g, 23.1 mmol) in MeCN (50 ml) was added Et₃N (3.84 ml, 0.03 mol), the mixture was stirred for 5 min (small exotherm), then warmed to 30 °C. The mixture was cooled to room temperature, diluted with EtOAc and washed saturated NH₄Cl, saturated NaHCO₃, and brine, then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was suspended in a mixture of isopropanol (10 ml) and toluene (100ml) and ammonium acetate (37g, 0.48 mol) was added, the reaction was refluxed for 4 h. Cooled to room temperature diluted with isopropyl acetate, washed with water, dried over Na₂SO₄, filtered, concentrated under reduced pressure and the residue was purified by column chromatography (50% to 100% EtOAc/Hexanes) to afford S5a (8.0 g, 90%) MS (ESI) m/z 368 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 7.61 (d, J = 8.1 Hz, 2H), 7.54 - 7.45 (m, 2H), 7.40 (s, 1H), 4.50 (s, 2H), 2.91 (s, 3H), 1.45 (d, J = 21.0 Hz, 9H).

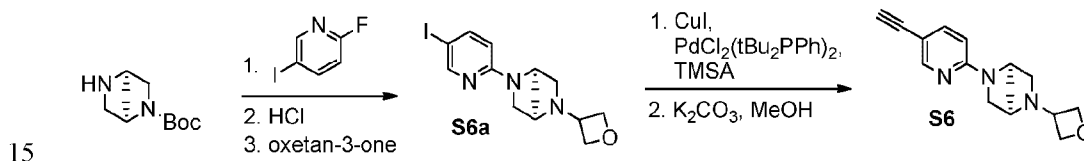
Synthesis of tert-butyl methyl((4-(4-((trimethylsilyl)ethynyl)phenyl)-1H-imidazol-2-yl)methyl)carbamate (S5b)

A solution of S5a (8 g, 0.02 mol), CuI (0.249 g, 1.0 mmol), PdCl₂(tBu₂PPh)₂ (0.408 g, 0.655 mmol), trimethylsilylacetylene (12.44 ml, 0.09 mol) in a mixture of CH₃CN/ Et₃N 3:1 (50 mL) was degassed with Argon for 10 min. The reaction mixture was heated to 65 °C overnight. The reaction was diluted with EtOAc and washed with NaHCO₃ solution and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was used for the next step without purification (5.85 g, 70%). MS (ESI) m/z 384.3 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 7.66 (d, J = 8.0 Hz, 2H), 7.45 - 7.31 (m, 3H), 4.84 (s, 2H), 2.91 (s, 4H), 1.46 (s, 9H), 0.23 (s, 9H).

Synthesis of 2-(4-ethynylphenyl)-7-methyl-7,8-dihydroimidazo[1,2-a]pyrazin-6(5H)-one (S5)

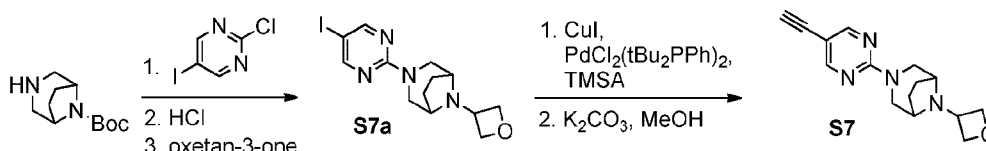
To an ice cooled solution of S5b (1450 mg, 0 mol) in 2-methyl tetrahydrofuran (3ml) was

added sodium hydride (60%, 0.21 g, 0.01 mol). After 10 min, methyl bromoacetate (0.72 ml, 0.01 mol) was added; the mixture was stirred for 5 min then warmed up to room temperature. After 30 min the reaction was diluted with EtOAc, rinsed with brine, dried over Na₂SO₄, filtered, concentrated under reduced pressure and the residue was purified by column chromatography (20% to 55% EtOAc/Hexanes). The product was dissolved in DCE (10ml) and HCl (4.0M in dioxane, 11.69 ml) warmed to 25 C. After 2 h the reaction was concentrated under vacuo. The residue was dissolved in DMF (10ml), Cesium carbonate (3.05 g, 0.01 mol) was added, warmed up 65 C for 45 min, cooled to room temperature added MeOH (10 mL), stir 25 min. Slowly dilute with ~40 mL water, stir 20 min. Filter off precipitated solids, rinsing with 30% MeOH in water. Concentrated under reduce pressure and the crude material was carried on without further purification (0.479 g, 62%) MS (ESI) m/z 252.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.69 (d, J = 8.0 Hz, 2H), 7.59 (s, 1H), 7.40 (d, J = 8.0 Hz, 2H), 4.65 (s, 2H), 4.56 (s, 2H), 4.11 (s, 1H), 2.95 (s, 3H).



Synthesis of (1R,4R)-2-(5-iodopyridin-2-yl)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptane (S6a) The title compound S6a was prepared according to the method presented for the synthesis of compound S1c but instead utilizing *tert*-butyl (1R,4R)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate. MS (ESI) m/z 358.0 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 8.25 (dd, J = 2.3, 0.8 Hz, 1H), 7.61 (ddd, J = 8.8, 2.3, 0.6 Hz, 1H), 6.18 (dd, J = 8.8, 0.8 Hz, 1H), 4.71 - 4.58 (m, 3H), 4.52 (t, J = 6.1 Hz, 1H), 4.45 (t, J = 5.9 Hz, 1H), 4.05 - 3.85 (m, 1H), 3.55 (d, J = 2.4 Hz, 1H), 3.43 - 3.18 (m, 2H), 2.94 (dd, J = 9.5, 2.0 Hz, 1H), 2.83 (dd, J = 9.4, 1.4 Hz, 1H), 2.00 - 1.89 (m, 1H), 1.89 - 1.80 (m, 1H), 1.39 (t, J = 7.3 Hz, 1H).

Synthesis of (1R,4R)-2-(5-ethynylpyridin-2-yl)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptane (S6) The title compound S6 was prepared according to the method presented for the synthesis of compound S1 but instead utilizing S6a. MS (ESI) m/z 256.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 8.13 (dd, J = 2.2, 0.9 Hz, 1H), 7.37 (dd, J = 8.7, 2.3 Hz, 1H), 6.23 - 5.98 (m, 1H), 4.54 (dt, J = 12.8, 6.5 Hz, 3H), 4.39 (t, J = 6.1 Hz, 1H), 4.32 (t, J = 5.9 Hz, 1H), 3.90 - 3.75 (m, 1H), 3.31 - 3.10 (m, 2H), 2.93 (s, 1H), 2.82 (dd, J = 9.5, 2.0 Hz, 1H), 2.73 - 2.60 (m, 1H), 1.82 (ddt, J = 9.7, 2.4, 1.2 Hz, 1H), 1.73 (ddt, J = 9.8, 2.5, 1.2 Hz, 1H).

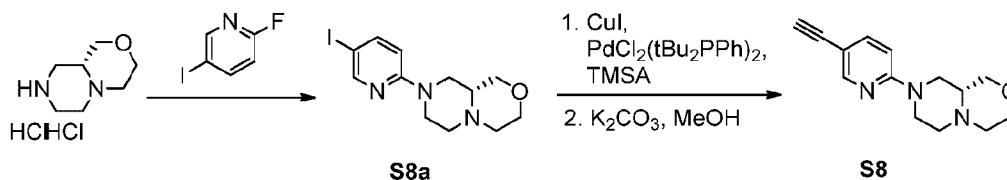


Synthesis of 3-(5-iodopyrimidin-2-yl)-8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octane (S7a)

- 5 The title compound **S7a** was prepared according to the method presented for the synthesis of compound **S1c** but instead utilizing 2-chloro-5-iodopyrimidine. MS (ESI) m/z 373.0 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.37 (s, 2H), 4.71 (t, J = 6.3 Hz, 2H), 4.59 (s, 2H), 4.21 (d, J = 12.4 Hz, 2H), 3.68 (s, 1H), 3.15 (s, 4H), 1.83 (s, 2H), 1.62 (s, 2H).

Synthesis of 3-(5-ethynylpyrimidin-2-yl)-8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octane (S7)

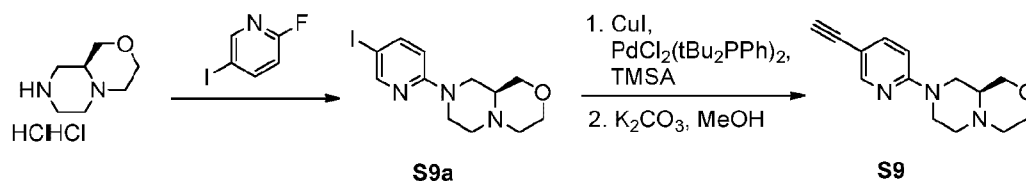
- 10 The title compound **S7** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S7a**. MS (ESI) m/z 271.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.38 (s, 1H), 4.71 (t, J = 6.2 Hz, 2H), 4.67 - 4.46 (m, 2H), 4.40 - 4.24 (m, 2H), 3.69 (p, J = 6.1 Hz, 1H), 3.29 - 3.10 (m, 4H), 1.89 - 1.73 (m, 2H), 1.74 - 1.47 (m, 2H).



15

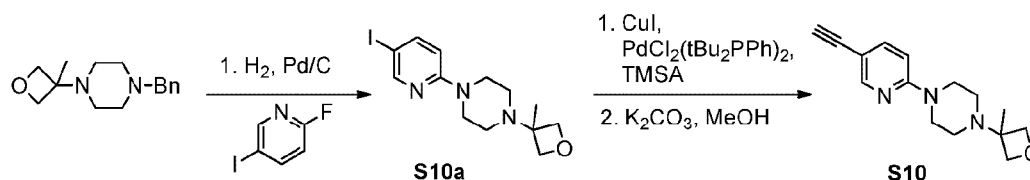
Synthesis of (R)-8-(5-iodopyridin-2-yl)octahydropyrazino[2,1-c][1,4]oxazine (S8a). The title compound **S8a** was prepared according to the method presented for the synthesis of compound **S1a** but instead utilizing (R)-octahydropyrazino[2,1-c][1,4]oxazine dihydrochloride. MS (ESI) m/z 346.1 $[M+H]^+$.

- 20 **Synthesis of (R)-8-(5-ethynylpyridin-2-yl) octahydropyrazino[2,1-c][1,4]oxazine (S8).** The title compound **S8** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S8a**. MS (ESI) m/z 244.2 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.30 (dd, J = 2.3, 0.8 Hz, 1H), 7.54 (dd, J = 8.8, 2.3 Hz, 1H), 6.56 (dd, J = 8.9, 0.8 Hz, 1H), 4.23 - 4.04 (m, 2H), 3.88 (dd, J = 11.4, 3.4 Hz, 1H), 3.81 (dd, J = 11.1, 3.1 Hz, 1H),
 25 3.73 (t, J = 11.5 Hz, 1H), 3.32 (t, J = 10.6 Hz, 1H), 3.13 - 3.01 (m, 2H), 2.86 (d, J = 11.4 Hz, 1H), 2.72 (d, J = 11.5 Hz, 1H), 2.54 (t, J = 11.7 Hz, 1H), 2.49 - 2.25 (m, 2H).



Synthesis of (S)-8-(5-iodopyridin-2-yl)octahydropyrazino[2,1-c][1,4]oxazine (S9a). The title compound **S9a** was prepared according to the method presented for the synthesis of compound **S1a** but instead utilizing (R)-octahydropyrazino[2,1-c][1,4]oxazine dihydrochloride. MS (ESI) m/z 346.1 [M+H]⁺.

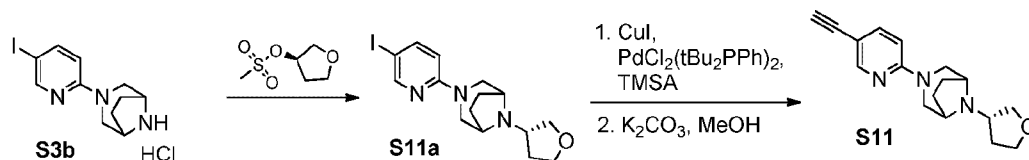
Synthesis of (S)-8-(5-ethynylpyridin-2-yl)octahydropyrazino[2,1-c][1,4]oxazine (S9). The title compound **S9** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S9a**. MS (ESI) m/z 244.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 8.30 (dd, J = 2.3, 0.8 Hz, 1H), 7.54 (dd, J = 8.8, 2.3 Hz, 1H), 6.56 (dd, J = 8.9, 0.8 Hz, 1H), 4.23 - 4.04 (m, 2H), 3.88 (dd, J = 11.4, 3.4 Hz, 1H), 3.81 (dd, J = 11.1, 3.1 Hz, 1H), 3.73 (t, J = 11.5 Hz, 1H), 3.32 (t, J = 10.6 Hz, 1H), 3.13 - 3.01 (m, 2H), 2.86 (d, J = 11.4 Hz, 1H), 2.72 (d, J = 11.5 Hz, 1H), 2.54 (t, J = 11.7 Hz, 1H), 2.49 - 2.25 (m, 2H).



1-(5-iodopyridin-2-yl)-4-(3-methyloxetan-3-yl)piperazine (S10a). 1-benzyl-4-(3-methyloxetan-3-yl)piperazine (6.75 g, 27.4 mmol), palladium (10% on carbon, 1.46 g, 1.37 mmol) in EtOH (55 ml) were combined in a PARR flask and shaken on the hydrogenator overnight at 45 PSI. The reaction was filtered over Celite, the filter cake was washed with 25% MeOH/DCM and the filtrate was concentrated under reduced pressure. The residue was combined 2-fluoro-5-iodopyridine to prepare the title compound **S10a** according to the method presented for the synthesis of compound **S1a**. MS (ESI) m/z 360.0 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 8.31 (d, J = 2.3 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 6.48 (d, J = 9.0 Hz, 1H), 4.62 (d, J = 5.5 Hz, 2H), 4.26 (d, J = 5.5 Hz, 2H), 3.54 (s, 4H), 2.44 (s, 5H), 1.37 (s, 3H).

1-(5-ethynylpyridin-2-yl)-4-(3-methyloxetan-3-yl)piperazine (S10). The title compound **S10** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S10a**. MS (ESI) m/z 258.0 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.18 (dd, J = 2.3, 0.8 Hz, 1H), 7.56 (dd, J = 8.9, 2.3 Hz, 1H), 6.76 (dd, J = 9.0, 0.8 Hz, 1H), 4.78 - 4.52 (m,

2H), 4.28 (d, $J = 5.9$ Hz, 2H), 3.65 - 3.48 (m, 4H), 3.43 (s, 1H), 2.59 - 2.39 (m, 4H), 1.38 (d, $J = 0.7$ Hz, 3H).

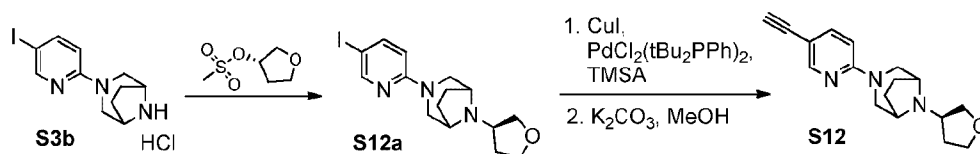


- 5 **Synthesis of 3-(5-iodopyridin-2-yl)-8-((S)-tetrahydrofuran-3-yl)-3,8-diazabicyclo[3.2.1]octane (S11a).** A solution of **S3b** (1.0 g, 3.173 mmol), (R)-tetrahydrofuran-3-yl methanesulfonate (965mg, 5.807 mmol), and potassium carbonate (1754 mg, 12.69 mmol) in CH_3CN (15 mL) was heated at reflux for 48 h. The reaction mixture cooled to room temperature, diluted with EtOAc and washed with brine. The organic extract was dried over
- 10 Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 5% MeOH/EtOAc) to afford **S11a** (355.2 mg, 29 %) MS (ESI) m/z 386.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.22 (dd, $J = 2.3, 0.7$ Hz, 1H), 7.56 (dd, $J = 8.9, 2.4$ Hz, 1H), 6.29 (dd, $J = 9.0, 0.7$ Hz, 1H), 3.96 - 3.84 (m, 2H), 3.76 (dt, $J = 8.6, 7.6$ Hz, 1H), 3.62 (ddd, $J = 11.5, 8.9, 2.5$ Hz, 2H), 3.55 (dd, $J = 8.2, 6.9$ Hz, 1H), 3.33 (d, $J = 4.7$ Hz,
- 15 1H), 3.20 (d, $J = 3.4$ Hz, 1H), 3.11 - 2.97 (m, 3H), 2.02 (dtd, $J = 12.1, 7.4, 4.7$ Hz, 1H), 1.95 - 1.87 (m, 2H), 1.87 - 1.72 (m, 1H), 1.67 - 1.56 (m, 2H).

Synthesis of 3-(5-ethynylpyridin-2-yl)-8-((S)-tetrahydrofuran-3-yl)-3,8-diazabicyclo[3.2.1]octane (S11).

- The title compound **S11** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S11a**. MS (ESI) m/z
- 20 284.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Methanol- d_4) δ 8.22 - 8.10 (m, 1H), 7.55 (dd, $J = 8.9, 2.3$ Hz, 1H), 6.65 (dd, $J = 9.1, 0.8$ Hz, 1H), 3.97 (td, $J = 8.1, 4.5$ Hz, 2H), 3.89 - 3.74 (m, 3H), 3.63 (dd, $J = 8.4, 6.6$ Hz, 1H), 3.48 (d, $J = 4.4$ Hz, 1H), 3.42 (s, 1H), 3.35 (s, 1H), 3.26 - 3.19 (m, 1H), 3.12 (dt, $J = 12.2, 3.5$ Hz, 2H), 2.15 (ddd, $J = 11.8, 8.2, 4.5$ Hz, 1H), 2.03 (dd, $J = 14.4, 7.3$ Hz, 2H), 1.85 (dq, $J = 12.0, 7.8$ Hz, 1H), 1.69 (d, $J = 9.1$ Hz, 2H).

25

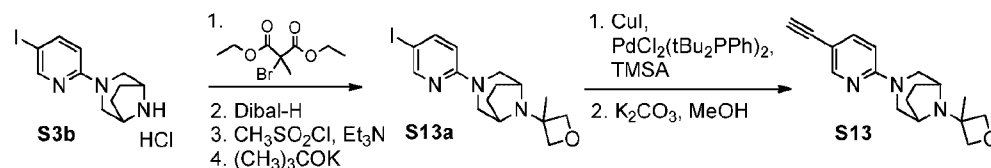


Synthesis of 3-(5-iodopyridin-2-yl)-8-((R)-tetrahydrofuran-3-yl)-3,8-diazabicyclo[3.2.1]octane (S12a). The title compound **S12a** was prepared according to the method presented for

the synthesis of compound **S11a** but instead utilizing (S)-tetrahydrofuran-3-yl methanesulfonate. MS (ESI) m/z 386.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.28 (d, J = 2.3 Hz, 1H), 7.62 (dd, J = 9.0, 2.4 Hz, 1H), 6.36 (d, J = 9.0 Hz, 1H), 4.04 - 3.91 (m, 2H), 3.90 - 3.75 (m, 1H), 3.68 (ddd, J = 11.6, 8.8, 2.5 Hz, 2H), 3.61 (dd, J = 8.2, 6.9 Hz, 1H), 3.39 (q, J = 2.7 Hz, 1H), 3.26 (dt, J = 5.0, 2.1 Hz, 1H), 3.18 - 3.04 (m, 3H), 2.17 - 2.01 (m, 1H), 1.97 (dd, J = 9.4, 5.6 Hz, 2H), 1.90 - 1.77 (m, 1H), 1.74 - 1.63 (m, 2H).

Synthesis of 3-(5-ethynylpyridin-2-yl)-8-((R)-tetrahydrofuran-3-yl)-3,8-diazabicyclo[3.2.1]octane (**S12**).

The title compound **S12** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S12a**. MS (ESI) m/z 284.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.22 - 8.07 (m, 1H), 7.55 (dd, J = 8.9, 2.3 Hz, 1H), 6.65 (dd, J = 8.8, 0.9 Hz, 1H), 3.96 (td, J = 8.1, 4.5 Hz, 2H), 3.88 - 3.74 (m, 3H), 3.63 (dd, J = 8.4, 6.6 Hz, 1H), 3.48 (s, 1H), 3.42 (s, 1H), 3.35 (s, 1H), 3.24 (t, J = 7.0 Hz, 1H), 3.12 (dt, J = 12.1, 3.4 Hz, 2H), 2.26 - 2.09 (m, 1H), 2.03 (dd, J = 14.1, 7.5 Hz, 2H), 1.85 (dq, J = 12.0, 8.0 Hz, 1H), 1.69 (d, J = 9.1 Hz, 2H).



Synthesis of 3-(5-iodopyridin-2-yl)-8-(3-methyloxetan-3-yl)-3,8-diazabicyclo[3.2.1]octane (**S13a**)

A suspension of **S3b** (3 g, 9.519 mmol), diethyl 2-bromo-2-methylmalonate (2.25 ml, 11.78 mmol), and sodium carbonate (1.19 g, 19.19 mmol) in NMP (30 mL) in a 100 ml sealed tube was stirred at 70 °C for 48 h. The reaction mixture was cooled to room temperature, diluted with EtOAc and washed with brine 2x. The organic extract was dried over Na_2SO_4 filtered, and the crude residue was purified by silica column chromatography (10% -20% EtOAc/ hexanes) to afford diethyl 2-(3-(5-iodopyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-methylmalonate (2.32 g, 50%). MS (ESI) m/z 488.0 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.27 (dd, J = 2.4, 0.7 Hz, 1H), 7.61 (dd, J = 9.0, 2.4 Hz, 1H), 6.51 - 6.27 (m, 1H), 4.37 - 4.07 (m, 4H), 3.84 (s, 2H), 3.79 - 3.72 (m, 2H), 3.29 - 3.07 (m, 2H), 1.77 - 1.63 (m, 4H), 1.62 (s, 3H), 1.27 (t, J = 7.2 Hz, 6H).

To a solution of diethyl 2-(3-(5-iodopyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-methylmalonate (907.9 mg, 1.863 mmol) in DCM (40 mL) at -78°C was added Dibal-H (1.0 M in toluene, 93 ml). The reaction was gradually warmed to room temperature and stirred

overnight. Dibal-H (1.0 M in DCM, 16 ml) was added, stirred for 1h, and then cooled to 0°C diluted with Et₂O. Slowly added water (4.4 mL), 15% NaOH (4.4 mL), followed by water (10.9 mL), warmed to room temperature and stirred for 15 min. Added Na₂SO₄, stirred for 15 min, then filtered off salts to give 2-(3-(5-iodopyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-methylpropane-1,3-diol (2.059 g, 65%). MS (ESI) m/z 404.0 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.18 (dd, J = 2.4, 0.7 Hz, 1H), 7.69 (dd, J = 9.0, 2.4 Hz, 1H), 6.54 (d, J = 9.1 Hz, 1H), 3.91 - 3.66 (m, 4H), 3.49 (s, 4H), 3.10 - 2.88 (m, 2H), 1.83 (d, J = 8.8 Hz, 2H), 1.72 (t, J = 6.6 Hz, 2H), 1.00 (s, 3H).

To a solution of 2-(3-(5-iodopyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-methylpropane-1,3-diol (2.06 g, 5.106 mmol) and triethylamine (1.5 ml, 10.76 mmol) in THF (25 mL) at 0°C was added methanesulfonyl chloride (0.40 ml, 5.169 mmol). The reaction was gradually warmed to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc and washed with brine. The organic extract was dried over Na₂SO₄, filtered, and the crude residue was purified by silica column chromatography (25% -50% EtOAc/ hexanes) to afford 3-chloro-2-(3-(5-iodopyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-methylpropan-1-ol (441.6 mg, 20.5%). MS (ESI) m/z 422.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 8.27 (dd, J = 2.4, 0.7 Hz, 1H), 7.62 (dd, J = 8.9, 2.4 Hz, 1H), 6.35 (dd, J = 9.0, 0.7 Hz, 1H), 4.63 (s, 1H), 3.90 - 3.63 (m, 4H), 3.56 (d, J = 5.1 Hz, 1H), 3.35 (s, 1H), 3.06 (dt, J = 11.8, 3.0 Hz, 2H), 2.87 (t, J = 13.5 Hz, 1H), 2.66 (d, J = 14.0 Hz, 1H), 1.88 (dt, J = 9.9, 4.9 Hz, 2H), 1.76 - 1.63 (m, 2H), 1.57 (s, 3H).

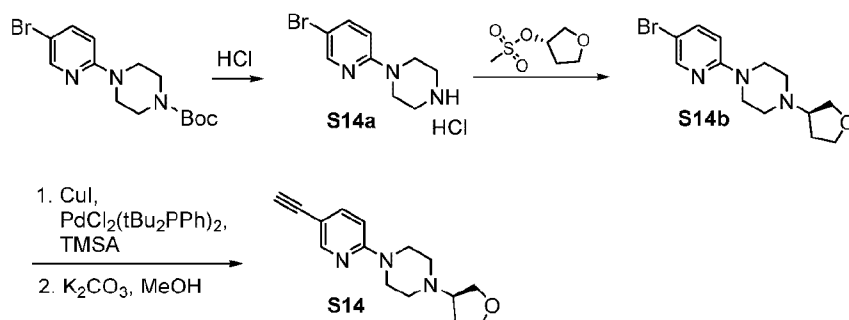
To a solution of 3-chloro-2-(3-(5-iodopyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-methylpropan-1-ol (418.5 mg, 0.992 mmol) in THF (10 mL) at 0°C, was added potassium tert-butoxide (1.0 M THF, 3 ml). After 10 min the reaction mixture was quenched with water, diluted with EtOAc and washed with brine. The organic extract was dried over Na₂SO₄, filtered, and the crude residue was purified by silica column chromatography (50% -100% EtOAc/ hexanes) to afford **S13a** (222.8 mg, 58% yield). MS (ESI) m/z 386.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 8.27 (dd, J = 2.4, 0.7 Hz, 1H), 7.61 (dd, J = 9.0, 2.4 Hz, 1H), 6.35 (dd, J = 9.0, 0.7 Hz, 1H), 3.68 (ddd, J = 11.5, 4.4, 2.6 Hz, 2H), 3.49 - 3.34 (m, 1H), 3.30 (q, J = 2.7 Hz, 1H), 3.07 (dd, J = 11.6, 2.5 Hz, 2H), 2.70 (dd, J = 5.0, 0.7 Hz, 1H), 2.64 - 2.53 (m, 2H), 2.39 (d, J = 13.2 Hz, 1H), 1.96 - 1.79 (m, 2H), 1.68 - 1.57 (m, 2H), 1.42 (d, J = 0.6 Hz, 3H).

Synthesis of 3-(5-ethynylpyridin-2-yl)-8-(3-methyloxetan-3-yl)-3,8-

diazabicyclo[3.2.1]octane (**S13**). The title compound **S13** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S13a**. MS (ESI) m/z 284.2 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.15 (dd, J = 2.3, 0.8 Hz, 1H), 7.53 (dd, J =

8.9, 2.3 Hz, 1H), 6.64 (dd, J = 9.0, 0.8 Hz, 1H), 3.91 - 3.74 (m, 3H), 3.50 - 3.43 (m, 1H), 3.42 (s, 1H), 3.39 - 3.32 (m, 1H), 3.08 (dt, J = 11.7, 1.9 Hz, 3H), 2.72 (dd, J = 4.9, 0.7 Hz, 2H), 2.66 (d, J = 13.3 Hz, 1H), 2.60 (d, J = 4.9 Hz, 1H), 2.43 (d, J = 13.3 Hz, 1H), 1.94 (dd, J = 9.4, 5.5 Hz, 3H), 1.69 - 1.57 (m, 2H), 1.42 (d, J = 0.6 Hz, 4H).

5



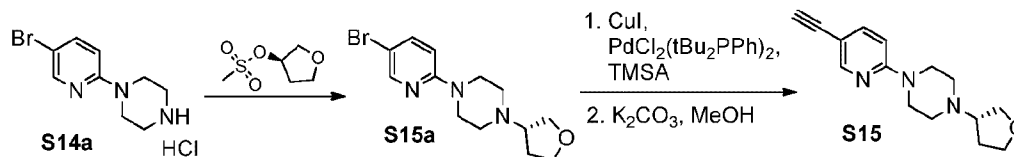
Synthesis of 1-(5-bromopyridin-2-yl)piperazine hydrochloride (S14a) To a solution of *tert*-butyl 4-(5-bromopyridin-2-yl)piperazine-1-carboxylate (5 g, 14.61 mmol) in DCM (60 mL) and MeOH (18 mL), was added HCl (4.0 M in dioxanes, 18 mL, 72 mmol). The reaction mixture was stirred at room temperature overnight. The reaction was diluted with DCM and washed with 2N NaOH. The aqueous layer was extracted with DCM 2x and the combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduce pressure to afford **S14a** (3.2 g, 90.4%). MS (ESI) *m/z* 242.1 ([M+H]⁺). ¹H NMR (400 MHz, Chloroform-d) δ 8.18 (dd, J = 2.6, 0.7 Hz, 1H), 7.52 (dd, J = 9.0, 2.6 Hz, 1H), 6.53 (dd, J = 9.1, 0.7 Hz, 1H), 3.54 - 3.40 (m, 4H), 3.09 - 2.87 (m, 4H).

Synthesis of (R)-1-(5-bromopyridin-2-yl)-4-(tetrahydrofuran-3-yl)piperazine (S14b). The title compound **S14a** was prepared according to the method presented for the synthesis of compound **S11a** but instead utilizing **S14a** and (S)-tetrahydrofuran-3-yl methanesulfonate. MS (ESI) *m/z* 312.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 8.19 (dd, J = 2.6, 0.7 Hz, 1H), 7.53 (dd, J = 9.0, 2.5 Hz, 1H), 6.54 (dd, J = 9.0, 0.7 Hz, 1H), 3.96 (td, J = 8.6, 4.4 Hz, 1H), 3.91 (dd, J = 8.7, 6.8 Hz, 1H), 3.80 (td, J = 8.4, 7.5 Hz, 1H), 3.69 (t, J = 7.7 Hz, 1H), 3.52 (t, J = 5.3 Hz, 4H), 3.01 (t, J = 7.3 Hz, 1H), 2.63 (d, J = 9.9 Hz, 2H), 2.57 - 2.46 (m, 2H), 2.07 (ddd, J = 9.9, 7.1, 3.3 Hz, 1H), 1.90 (q, J = 11.1, 9.5 Hz, 1H).

Synthesis of (R)-1-(5-ethynylpyridin-2-yl)-4-(tetrahydrofuran-3-yl)piperazine (S14). The title compound **S14** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S14b**. MS (ESI) *m/z* 258.1 [M+H]⁺. ¹H NMR (400 MHz,

Methanol-d₄) δ 8.18 (d, J = 2.3 Hz, 1H), 7.56 (dd, J = 8.8, 2.3 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 3.95 (dt, J = 8.5, 4.3 Hz, 1H), 3.90 (dd, J = 8.8, 7.0 Hz, 2H), 3.76 (q, J = 8.2 Hz, 1H), 3.68 (dd, J = 8.8, 6.6 Hz, 1H), 3.58 (t, J = 5.2 Hz, 4H), 3.43 (s, 1H), 3.09 - 2.97 (m, 1H), 2.65 (dt, J = 10.6, 5.2 Hz, 2H), 2.54 (dt, J = 11.2, 5.2 Hz, 2H), 2.20 - 2.06 (m, 1H), 1.96 - 1.83 (m, 1H).

5



Synthesis of (S)-1-(5-bromopyridin-2-yl)-4-(tetrahydrofuran-3-yl)piperazine (S15a). The

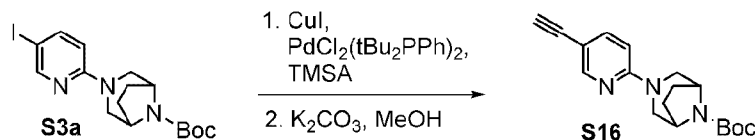
title compound **S15a** was prepared according to the method presented for the synthesis of compound **S11a** but instead utilizing **S14a**. MS (ESI) m/z 312.2 $[M+H]^+$. ¹H NMR (400 MHz,

10 Chloroform-d) δ 8.18 (dd, J = 2.6, 0.7 Hz, 1H), 7.52 (dd, J = 9.0, 2.6 Hz, 1H), 6.53 (dd, J = 9.1, 0.7 Hz, 1H), 3.96 (td, J = 8.6, 4.4 Hz, 1H), 3.91 (dd, J = 8.6, 6.8 Hz, 1H), 3.80 (td, J = 8.4, 7.5 Hz, 1H), 3.68 (dd, J = 8.7, 6.7 Hz, 1H), 3.52 (dd, J = 5.9, 4.5 Hz, 4H), 3.00 (p, J = 7.1 Hz, 1H), 2.63 (dt, J = 10.7, 5.2 Hz, 2H), 2.50 (dt, J = 10.8, 5.1 Hz, 2H), 2.17 - 1.99 (m, 1H), 1.99 - 1.79 (m, 1H).

15 **Synthesis of (S)-1-(5-ethynylpyridin-2-yl)-4-(tetrahydrofuran-3-yl)piperazine (S15).** The

title compound **S15** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S15a**. MS (ESI) m/z 258.1 $[M+H]^+$. ¹H NMR (400 MHz,

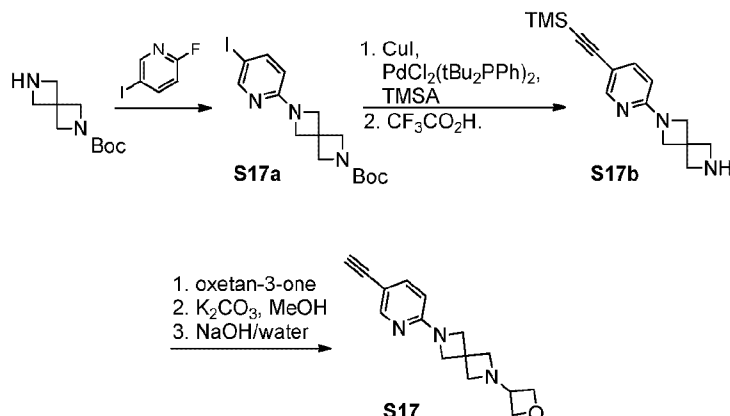
20 Methanol-d₄) δ 8.09 (dd, J = 2.4, 0.8 Hz, 1H), 7.47 (dd, J = 8.9, 2.3 Hz, 1H), 6.66 (dd, J = 9.0, 0.8 Hz, 1H), 3.86 (dt, J = 8.6, 4.3 Hz, 1H), 3.80 (dd, J = 8.9, 7.0 Hz, 2H), 3.67 (td, J = 8.4, 7.2 Hz, 1H), 3.59 (dd, J = 8.7, 6.6 Hz, 1H), 3.49 (t, J = 5.2 Hz, 4H), 3.34 (s, 1H), 3.02 - 2.86 (m, 1H), 2.55 (dt, J = 10.7, 5.2 Hz, 2H), 2.44 (dt, J = 11.1, 5.2 Hz, 2H), 2.10 - 1.94 (m, 2H), 1.86 - 1.71 (m, 2H).



25 **Synthesis of tert-butyl 3-(5-ethynylpyridin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-**

carboxylate (S16). The title compound **S16** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S3a**. MS (ESI) m/z 313.9 $[M+H]^+$. ¹H NMR (400 MHz, Methanol-d₄) δ 8.18 (dd, J = 2.3, 0.8 Hz, 1H), 7.56 (dd, J = 8.9, 2.3 Hz, 1H), 6.69 (dd, J = 8.9, 0.9 Hz, 1H), 4.45 - 4.30 (m, 2H), 4.04 - 3.95 (m, 2H), 3.43 (s, 1H), 3.02 (d, J = 12.2

Hz, 2H), 1.94 (dd, $J = 8.7, 4.4$ Hz, 2H), 1.75 (d, $J = 7.3$ Hz, 2H), 1.48 (s, 9H).



Synthesis of tert-butyl 6-(5-iodopyridin-2-yl)-2-azaspiro[3.3]heptane-2-carboxylate (**S17a**).

The title compound **S17a** was prepared according to the method presented for the synthesis of compound **S1a** but instead utilizing *tert*-Butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate. MS (ESI) m/z 401.9 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.28 (d, $J = 2.2$ Hz, 1H), 7.67 (d, $J = 8.7$ Hz, 1H), 6.14 (d, $J = 8.7$ Hz, 1H), 4.13 (s, 4H), 4.10 (s, 4H), 1.44 (s, 9H).

Synthesis of 6-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)-2-azaspiro[3.3]heptane (**S17b**). A

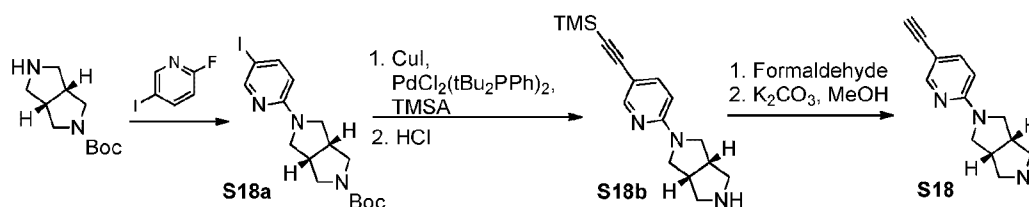
solution of **S17a** (1.048 mg, 2.612 mmol), CuI (0.111 g, 0.583 mmol), $\text{PdCl}_2(\text{tBu}_2\text{PPh})_2$ (0.163 g, 0.261 mmol), TMSA (2.1 ml, 14.75 mmol), Et_3N (2.7 ml, 19.48 mmol) in CH_3CN (20 mL) at 0°C was degassed with Argon for 10 min. The reaction mixture stirred at reflux overnight, then cooled to room temperature, diluted with EtOAc, washed with NaHCO_3 solution and dried over Na_2SO_4 , filtered, concentrated under reduced pressure and the residue was purified by silica column chromatography (20% to 40% EtOAc/Hex) to give (760 mg, 78%) of desired product.

This product (0.4 g, 1076.58 μmol) was dissolved in DCM (5 mL) and trifluoroacetic acid (1000 μl , 13.07 mmol) was added, the mixture was stirred at 0°C . After 4 h, the reaction mixture was concentrated under reduced pressure, diluted with toluene (5 mL) and concentrated to afford **S17b** (0.54 g, 100.1%). MS (ESI) m/z 272.1 $[\text{M}+\text{H}]^+$.

Synthesis of 6-(5-ethynylpyridin-2-yl)-2-(oxetan-3-yl)-2-azaspiro[3.3]heptane (**S17**)

A suspension of **S17b** (538 mg, 1.08 mmol) with triethylamine (0.3 ml, 2.154 mmol) in 2-Me THF (4 mL) and AcOH (0.2 mL), was added oxetan-3-one (234 mg, 3.247 mmol) in 2-Me-THF (1 mL) followed by sodium cyanoborohydride (209 mg, 3.326 mmol). The reaction was stirred at room temperature. After 18 h, the reaction mixture was quenched with NaHCO_3 solution and partitioned with EtOAc. The organic extract was dried over Na_2SO_4 , filtered, concentrated under reduced pressure and the residue was purified by silica column chromatography (50% to 75 % EtOAc/Hex). The product was dissolved in MeOH (5 mL), Potassium carbonate (0.28 g, 2.05

mmol) was added and the mixture was stirred at room temperature. After 48h the reaction mixture was concentrated under reduced pressure, diluted with EtOAc, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was dissolved in methanol (2.0 mL) and sodium hydroxide solution (2M, 2 mL) was added, warmed up to 70°C for 18 h. The reaction was cooled to room temperature concentrated under reduced pressure; the residue was diluted with EtOAc, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford **S17** MS (ESI) m/z 256.1 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.09 (dd, J = 2.2, 0.8 Hz, 1H), 7.55 (dd, J = 8.7, 2.2 Hz, 1H), 6.36 (dd, J = 8.7, 0.8 Hz, 1H), 4.72 (td, J = 6.7, 0.5 Hz, 3H), 4.45 (ddd, J = 6.8, 4.9, 0.6 Hz, 3H), 4.13 (s, 5H), 3.76 (tt, J = 6.5, 4.9 Hz, 1H), 3.50 (s, 5H), 3.44 (s, 1H).



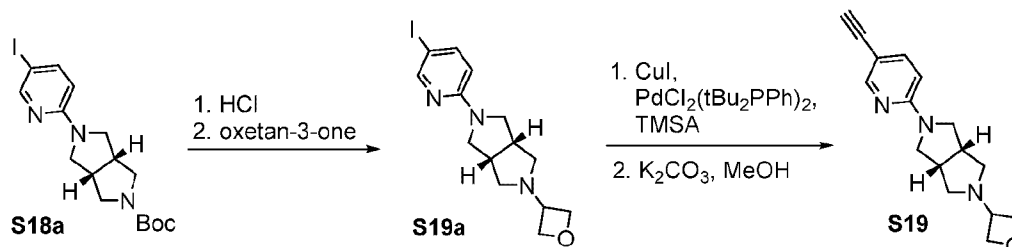
Synthesis of tert-butyl (3aR,6aS)-5-(5-iodopyridin-2-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (S18a) The title compound **S18a** was prepared according to the method presented for the synthesis of compound **S1a** but instead utilizing *tert*-butyl (3aR,6aS)-hexahydropyrrolo [3,4-c]pyrrole-2(1H)-carboxylate. MS (ESI) m/z 415.8 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 8.28 (dd, J = 2.4, 0.8 Hz, 1H), 7.63 (dd, J = 8.9, 2.3 Hz, 1H), 6.19 (d, J = 8.9 Hz, 1H), 3.66 (dd, J = 10.7, 7.0 Hz, 4H), 3.51 - 3.17 (m, 4H), 2.99 (d, J = 5.9 Hz, 2H), 1.45 (s, 9H).

Synthesis of (3aR,6aS)-2-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)octahydropyrrolo[3,4-c]pyrrole (S18b). A solution of **S18a** (0.986 g, 2.374 mmol), CuI (0.099 g, 0.522 mmol), PdCl₂(tBu₂PPh)₂ (0.148 g, 0.237 mmol), TMSA (1.9 mL, 13.35 mmol), Et₃N (2.5 mL, 18.04 mmol) in CH₃CN (8 mL) was degassed with Argon for 10 min. The reaction mixture was heated to 60°C and stirred overnight. The reaction was diluted with EtOAc and washed with NaHCO₃ solution, dried over Na₂SO₄, filtered, and concentrated under reduced pressure and the residue was purified by silica column chromatography (10% to 30 %EtOAc/Hex), the product (0.68 g, 1.75 mmol) was dissolved in a mixture of DCM (8 mL) and MeOH (2 mL) and HCl (4.0 M in dioxanes, 2 mL) was added. The reaction was stirred for 18 h, diluted with DCM, washed with 2N NaOH solution. The aqueous layer was re-extracted with DCM and the combined organic extracts were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford

S18b (0.56 g, 112.7%). MS (ESI) m/z 286.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 7.82 (dd, J = 2.1, 0.7 Hz, 1H), 7.73 (dd, J = 9.5, 2.1 Hz, 1H), 6.88 (dd, J = 9.5, 0.9 Hz, 1H), 3.78 - 3.63 (m, 2H), 3.59 - 3.48 (m, 2H), 3.46 - 3.34 (m, 3H), 3.25 - 3.10 (m, 3H), -0.00 (s, 9H).

Synthesis of (3aR,6aS)-2-(5-ethynylpyridin-2-yl)-5-methyloctahydropyrrolo[3,4-c]pyrrole

- 5 **(S18)**. To a solution of **S18b** (0.25 g, 0.701 mmol) in DCE (6 mL) was added formaldehyde solution (0.30 mL, 8.143 mmol) and acetic acid (0.025 mL, 4.367 mmol). The reaction mixture was heated at 60°C for 30 min. Cooled to room temperature and added sodium cyanoborohydride (165.1 mg, 2.63 mmol). The reaction was heated at 60°C for 45 min, then cooled to room temperature, diluted with EtOAc, washed with brine, back-extracted the aqueous layer with EtOAc, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure the residue was dissolved in MeOH (5 mL) and Potassium carbonate (0.29 g, 2.1 mmol) was added, the reaction mixture was stirred at room temperature. After 18 h, the reaction was concentrated under reduced pressure and the residue was diluted with EtOAc, washed with brine dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to afford **S18** (0.15 g, 87%). MS (ESI) m/z 228.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.19 (dd, J = 2.3, 0.8 Hz, 1H), 7.60 (dd, J = 8.8, 2.3 Hz, 1H), 6.58 (dd, J = 8.9, 0.8 Hz, 1H), 3.70 - 3.59 (m, 1H), 3.54 - 3.45 (m, 3H), 3.10 (s, 3H), 2.97 - 2.84 (m, 2H), 2.54 (dd, J = 9.7, 4.0 Hz, 2H), 2.39 (s, 3H).



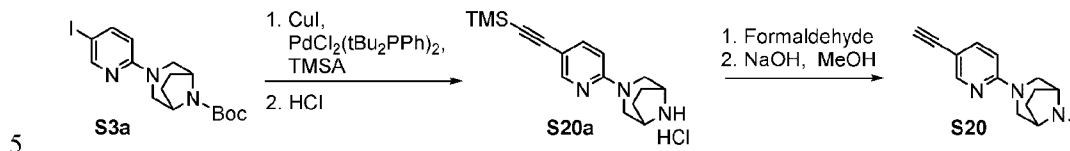
Synthesis of (3aR,6aS)-2-(5-iodopyridin-2-yl)-5-(oxetan-3-yl)octahydropyrrolo[3,4-

- 20 **c]pyrrole (S19a)** The title compound **S19a** was prepared according to the method presented for the synthesis of compound **S1c** but instead utilizing **S18a**. MS (ESI) m/z 372.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.17 (dd, J = 2.3, 0.7 Hz, 1H), 7.71 (ddd, J = 8.9, 2.3, 0.8 Hz, 1H), 6.43 (dd, J = 9.0, 0.7 Hz, 1H), 4.69 (t, J = 6.6 Hz, 2H), 4.64 - 4.55 (m, 2H), 3.70 - 3.60 (m, 1H), 3.59 - 3.49 (m, 2H), 3.38 (dd, J = 10.8, 3.1 Hz, 2H), 3.02 (td, J = 7.3, 3.7 Hz, 2H), 2.88 - 2.71 (m, 2H), 2.42 (dd, J = 9.4, 4.0 Hz, 2H).

Synthesis of (3aR,6aS)-2-(5-ethynylpyridin-2-yl)-5-(oxetan-3-yl)octahydropyrrolo[3,4-

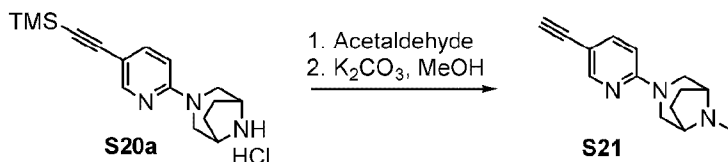
c]pyrrole (S19). The title compound **S19** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S19a**. MS (ESI) m/z 270.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.05 (dd, J = 2.2, 0.8 Hz, 1H), 7.46 (dd, J = 8.8, 2.3 Hz, 1H),

6.43 (dd, $J = 8.9, 0.8$ Hz, 1H), 4.68 - 4.58 (m, 2H), 4.59 - 4.44 (m, 2H), 3.64 - 3.45 (m, 2H), 3.40 - 3.30 (m, 4H), 2.95 (dq, $J = 7.5, 3.9$ Hz, 2H), 2.70 (dd, $J = 9.6, 7.1$ Hz, 1H), 2.36 (dd, $J = 9.5, 4.0$ Hz, 2H).



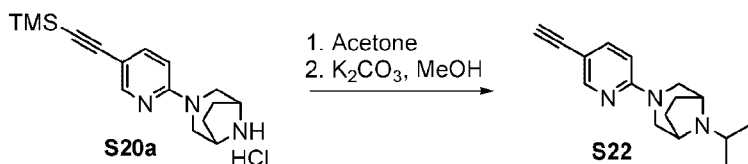
Synthesis of 3-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)-3,8-diazabicyclo[3.2.1]octane hydrochloride (S20a) The title compound **S20a** was prepared according to the method presented for the synthesis of compound **S19a** but instead utilizing **S3a**. MS (ESI) m/z 286.1 $[M+H]^+$.

- 10 **Synthesis of 3-(5-ethynylpyridin-2-yl)-8-methyl-3,8-diazabicyclo[3.2.1]octane (S20)** To a solution of **S20a** (0.2 g, 0.7 mmol) in THF (6 mL) was added formaldehyde solution (0.13 mL, 3.5 mmol) and acetic acid (0.03 mL, 0.51 mmol). The reaction mixture stirred at room temperature overnight. Sodium cyanoborohydride (132.09 mg, 2.1 mmol) was added. After 5 h, MeOH (2 mL) and NaOH (2 N, 2 mL) were added and the mixture was stirred for another 18 h.
- 15 The reaction was concentrated under reduced pressure, diluted with EtOAc, washed with brine, back-extracted the aqueous layer with EtOAc, dried over Na_2SO_4 , filtered, concentrated under reduced pressure and the residue was purified by silica column chromatography (100% EtOAc to 5% - 10% MeOH / EtOAc) to give **S20** (62.6 mg, 39.3%). MS (ESI) m/z 228.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.16 (dd, $J = 2.4, 0.8$ Hz, 1H), 7.55 (dd, $J = 8.9, 2.3$ Hz, 1H), 6.66 (dd, $J = 8.9, 0.9$ Hz, 1H), 3.86 (dd, $J = 12.5, 2.4$ Hz, 3H), 3.42 (s, 1H), 3.08 (dd, $J = 12.3, 2.3$ Hz, 3H), 2.36 (d, $J = 2.4$ Hz, 3H), 2.07 (dt, $J = 7.1, 3.2$ Hz, 2H), 1.68 (t, $J = 6.8$ Hz, 2H).
- 20



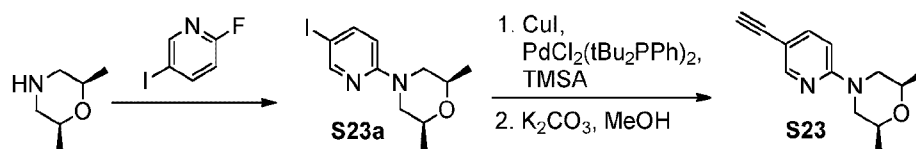
- 25 **Synthesis of 8-ethyl-3-(5-ethynylpyridin-2-yl)-3,8-diazabicyclo[3.2.1]octane (S21)** To a solution of **S20a** (0.24 g, 0.83 mmol) in THF (5 mL) and MeOH (2 mL) was added acetaldehyde (0.5 mL, 8.90 mmol) and acetic acid (0.04 mL, 0.7 mmol). After 18 h sodium cyanoborohydride (314 mg, 5.0 mmol) was added. Stirred overnight, diluted with EtOAc, washed with brine, back-

extracted the aqueous layer with EtOAc, dried over Na₂SO₄, filtered, and concentrated under reduced pressure and the residue was purified by silica column chromatography (10% - 20% MeOH / EtOAc) to give (0.12 g, 0.39 mmol) of product which was dissolved in MeOH (5 mL) and potassium carbonate (0.16 g, 1.17 mmol) was added, the reaction mixture was stirred at room temperature. After 3 h, the reaction was concentrated under reduced pressure and the residue was diluted with EtOAc, washed with brine dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford **S21** (0.09 g, 44%). MS (ESI) m/z 242.2 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.16 (dd, J = 2.3, 0.8 Hz, 1H), 7.55 (dd, J = 8.9, 2.3 Hz, 1H), 6.65 (dd, J = 8.9, 0.9 Hz, 1H), 3.85 (dd, J = 12.5, 2.4 Hz, 2H), 3.44 (dd, J = 4.6, 2.5 Hz, 2H), 3.41 (s, 1H), 3.09 (dd, J = 12.2, 2.2 Hz, 2H), 2.52 (q, J = 7.2 Hz, 2H), 2.00 (dt, J = 7.0, 3.1 Hz, 2H), 1.67 (t, J = 6.8 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H).



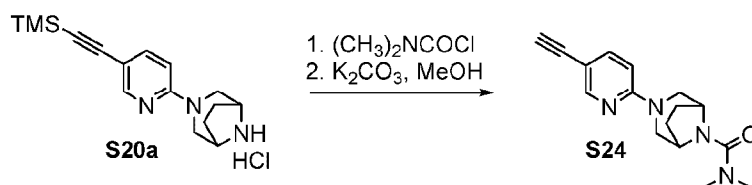
15 **Synthesis of 3-(5-ethynylpyridin-2-yl)-8-isopropyl-3,8-diazabicyclo[3.2.1]octane (S22)**

To a solution of **S20a** (0.1 g, 0.35 mmol) in Methanol (1.2 ml) was added sodium acetate (28.74 mg, 0.35 mmol), acetic acid (21.04 mg, 0.35 mmol) and acetone (20.35 mg, 0.35 mmol) the mixture was stirred at 40°C. After 1 h sodium cyanoborohydride (44.03 mg, 0.7 mmol) was added and the reaction was stirred at 40°C. After 12 h the mixture was cooled to room temperature, concentrated under reduce pressure and the residue was diluted with EtOAc, washed with saturated NaHCO₃ solution, dried over Na₂SO₄, filtered, and concentrated under reduced pressure and purified by silica column chromatography (2% MeOH / EtOAc). The product was dissolved in Methanol (1 ml), potassium carbonate (0.05 g, 0.35 mmol) was added and after 1 h the mixture was concentrated diluted with EtOAc, washed with water, dried over Na₂SO₄, filtered concentrated to yield **S22** (28 mg, 31.3%). MS (ESI) m/z 256.2 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.18 (d, J = 2.3 Hz, 1H), 7.57 (dd, J = 8.9, 2.4 Hz, 1H), 6.68 (d, J = 8.9 Hz, 1H), 3.93 – 3.68 (m, 6H), 3.43 (s, 1H), 3.23 – 3.12 (m, 3H), 2.86 (s, 2H), 2.07 – 1.92 (m, 3H), 1.75 (t, J = 6.6 Hz, 3H), 1.20 (d, J = 6.4 Hz, 8H).

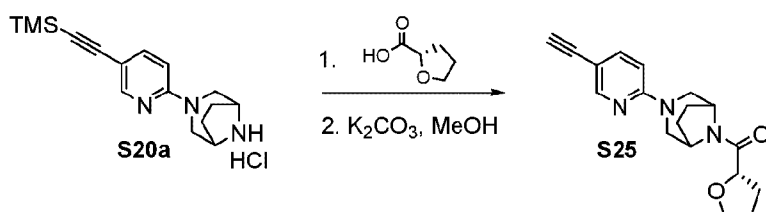


Synthesis of (2S,6R)-4-(5-iodopyridin-2-yl)-2,6-dimethylmorpholine (S23a) The title compound **S23a** was prepared according to the method presented for the synthesis of compound **S1a** but instead utilizing (2S,6R)-2,6-dimethylmorpholine. MS (ESI) *m/z* 319.0 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 8.32 (d, *J* = 2.3 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 6.49 (d, *J* = 9.0 Hz, 1H), 4.00 (d, *J* = 12.6 Hz, 2H), 3.70 (ddd, *J* = 10.6, 6.3, 2.6 Hz, 2H), 2.53 (t, *J* = 11.6 Hz, 2H), 1.26 (d, *J* = 6.2 Hz, 6H).

Synthesis of (2S,6R)-4-(5-ethynylpyridin-2-yl)-2,6-dimethylmorpholine (S23) The title compound **S23** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S23a**. MS (ESI) *m/z* 217.1 [M+H]⁺.



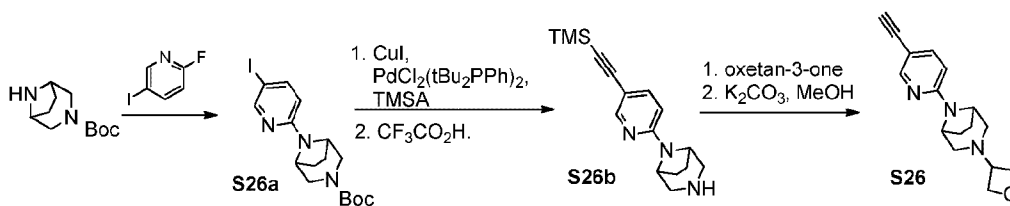
Synthesis of 3-(5-ethynylpyridin-2-yl)-N,N-dimethyl-3,8-diazabicyclo[3.2.1]octane-8-carboxamide (S24) To a solution of **S20a** (200 mg, 0.558 mmol) and Et₃N (0.3 ml, 2.164 mmol) in DCM (5 mL) at 0°C, was added dimethylcarbamoyl chloride (0.055 ml, 0.601 mmol). The reaction was gradually warmed to room temperature and stirred overnight. The reaction was concentrated under reduced pressure. The residue was dissolved in MeOH (5 mL) and K₂CO₃ (313 mg, 2.236 mmol) was added. After stirring at room temperature for 48 h, the reaction was concentrated, then diluted with EtOAc and washed with brine. The organic extracts were dried over Na₂SO₄ to give **S24** (123.9 mg, 78%). MS (ESI) *m/z* 276.2 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.17 (dd, *J* = 2.3, 0.8 Hz, 1H), 7.55 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.69 (dd, *J* = 9.0, 0.8 Hz, 1H), 4.19 (dd, *J* = 4.5, 2.2 Hz, 3H), 3.98 (dd, *J* = 12.4, 2.5 Hz, 3H), 3.42 (s, 1H), 3.11 (dd, *J* = 12.2, 2.1 Hz, 3H), 2.94 (s, 8H), 1.88 (dd, *J* = 8.5, 4.4 Hz, 3H), 1.71 (q, *J* = 6.7 Hz, 2H).



Synthesis of (3-(5-ethynylpyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)((S)-

tetrahydrofuran-2-yl)methanone (S25) To **S20a** suspended in CH_2Cl_2 (10 mL) was added (S)-

- 5 tetrahydrofuran-2-carboxylic acid (0.12 mL, 1 mmol), Et_3N (0.68 mL, 5 mmol) followed by HATU (0.48 g, 1 mmol). The mixture was stirred for 1.5 h. The mixture was diluted with DCM and washed with water. The organic layer was dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was dissolved in MeOH (20 mL), cooled to 5 °C and potassium carbonate (0.4 g, 3 mmol) was added. After 30 min, the reaction quenched with water and brine, extracted into
- 10 DCM, dried over Na_2SO_4 , filtered, concentrated under reduced pressure and the residue was purified by silica column chromatography (60% - 100% EtOAc/hexanes to 5% MeOH / EtOAc) to give **S25** (0.23 g, 74.3%). MS (ESI) m/z 312.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.29 (dd, J = 2.3, 0.8 Hz, 1H), 7.54 (dt, J = 8.9, 2.4 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 4.84 (t, J = 8.6 Hz, 1H), 4.66 (d, J = 6.8 Hz, 1H), 4.56 (ddd, J = 14.9, 7.4, 5.7 Hz, 2H), 4.12 (ddd, J =
- 15 20.9, 12.7, 2.3 Hz, 1H), 3.99 - 3.73 (m, 4H), 3.21 (dd, J = 12.1, 2.3 Hz, 1H), 3.14 (dd, J = 12.0, 2.4 Hz, 1H), 3.07 (s, 1H), 3.06 - 3.02 (m, 0H), 2.41 - 2.21 (m, 1H), 2.15 - 1.70 (m, 5H).



Synthesis of tert-butyl 8-(5-iodopyridin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

- 20 (**S26a**) The title compound **S26a** was prepared according to the method presented for the synthesis of compound **S1a** but instead utilizing tert-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate. MS (ESI) m/z 415.8 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.31 (d, J = 2.2 Hz, 1H), 7.70 (s, 1H), 6.46 (s, 1H), 4.45 (s, 2H), 3.78 (d, J = 52.7 Hz, 2H), 3.14 (dd, J = 50.9, 12.9 Hz, 2H), 2.06 - 1.77 (m, 4H), 1.45 (s, 12H).

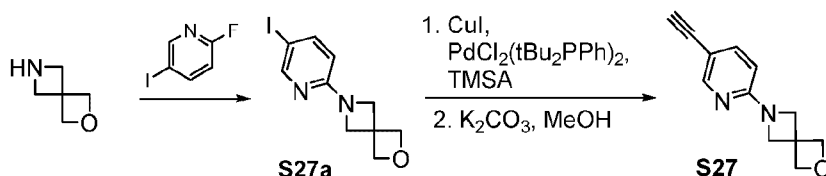
- 25 **Synthesis of 8-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)-3,8-diazabicyclo[3.2.1]octane (S26b).** The title compound **S26b** was prepared according to the method presented for the

synthesis of compound **S17b** but instead utilizing **S26a**. MS (ESI) m/z 286.2 $[M+H]^+$.

Synthesis of 8-(5-ethynylpyridin-2-yl)-3-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octane (S26).

The title compound **S26** was prepared according to the method presented for the synthesis of compound **S18** but instead utilizing oxetan-3-one. MS (ESI) m/z 270.2 $[M+H]^+$. 1H NMR (400

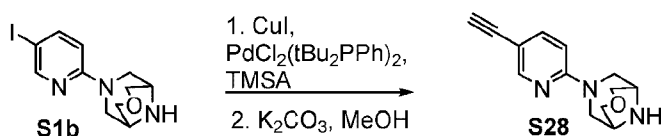
- 5 MHz, Methanol- d_4) δ 8.18 (d, J = 2.3 Hz, 1H), 7.58 (dd, J = 8.8, 2.3 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 4.61 (dt, J = 11.1, 5.5 Hz, 7H), 3.51 - 3.44 (m, 2H), 2.64 (dd, J = 10.9, 2.6 Hz, 3H), 2.23 (d, J = 10.7 Hz, 2H), 2.14 (t, J = 6.2 Hz, 2H), 1.99 (dd, J = 8.3, 4.2 Hz, 2H).



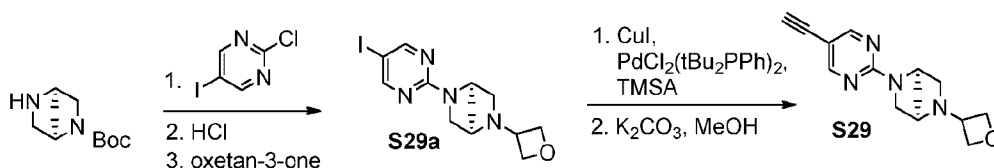
- 10 **Synthesis of 5-iodo-2-(2-oxaspiro[3.3]heptan-6-yl)pyridine (S27a).** The title compound **S27a** was prepared according to the method presented for the synthesis of compound **S1a** but instead utilizing 2-oxa-6-azaspiro[3.3]heptane. 1H NMR (400 MHz, Chloroform- d) δ 8.16 (dd, J = 2.4, 0.7 Hz, 1H), 7.52 (dd, J = 8.8, 2.4 Hz, 1H), 6.20 (d, J = 8.8 Hz, 1H), 4.84 (s, 4H), 4.17 (s, 5H).

Synthesis of 7-(5-ethynylpyridin-2-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane (S27). The title compound **S27**

- 15 was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S27a**. MS (ESI) m/z 201.1 $[M+H]^+$.



- 20 **Synthesis of 7-(5-ethynylpyridin-2-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane (S28).** The title compound **S28** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S1b**. MS (ESI) m/z 230.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.25 (s, 1H), 7.56 - 7.43 (m, 1H), 6.48 (d, J = 8.9 Hz, 1H), 4.42 (d, J = 13.5 Hz, 2H), 4.12 (d, J = 12.1 Hz, 2H), 3.93 (d, J = 12.2 Hz, 2H), 3.59 (d, J = 13.6 Hz, 2H), 3.36 (s, 2H), 3.00 (d, J =
- 25 1.1 Hz, 1H).



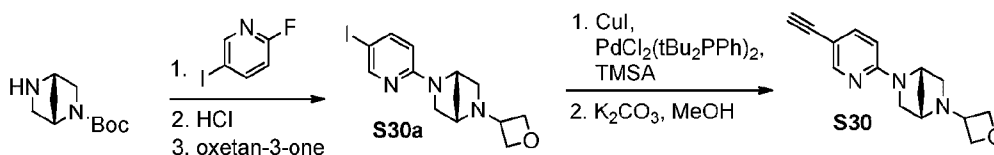
Synthesis of (1R,4R)-2-(5-iodopyrimidin-2-yl)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]

heptane (S29a) The title compound **S29a** was prepared according to the method presented for the synthesis of compound **S7a** but instead utilizing tert-butyl (1R,4R)-2,5-

- 5 diazabicyclo[2.2.1]heptane-2-carboxylate. MS (ESI) m/z 359.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.37 (s, 2H), 4.79 (s, 1H), 4.69 (dt, J = 10.0, 6.5 Hz, 2H), 4.55 (t, J = 6.1 Hz, 1H), 4.48 (t, J = 5.9 Hz, 1H), 3.98 (p, J = 6.3 Hz, 1H), 3.57 (s, 1H), 3.46 (dd, J = 11.0, 1.6 Hz, 1H), 3.36 (dd, J = 10.8, 2.0 Hz, 1H), 2.98 (dd, J = 9.6, 2.0 Hz, 1H), 2.82 (d, J = 9.6 Hz, 1H), 1.97 (d, J = 9.9 Hz, 1H), 1.86 (d, J = 9.8 Hz, 1H).

10 Synthesis of (1R,4R)-2-(5-ethynylpyridin-2-yl)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]

heptane (S29) The title compound **S29** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S29a**. MS (ESI) m/z 257.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.39 (s, 2H), 4.88 (s, 1H), 4.70 (dt, J = 9.5, 6.5 Hz, 2H), 4.52 (dt, J = 26.3, 6.0 Hz, 2H), 3.99 (p, J = 6.3 Hz, 1H), 3.58 (s, 1H), 3.52 (d, J = 10.9 Hz, 1H), 3.41 (dd, J = 11.0, 2.0 Hz, 1H), 3.18 (s, 1H), 2.99 (d, J = 9.6 Hz, 1H), 2.83 (d, J = 9.6 Hz, 1H), 1.98 (d, J = 9.9 Hz, 1H), 1.87 (d, J = 9.8 Hz, 1H).



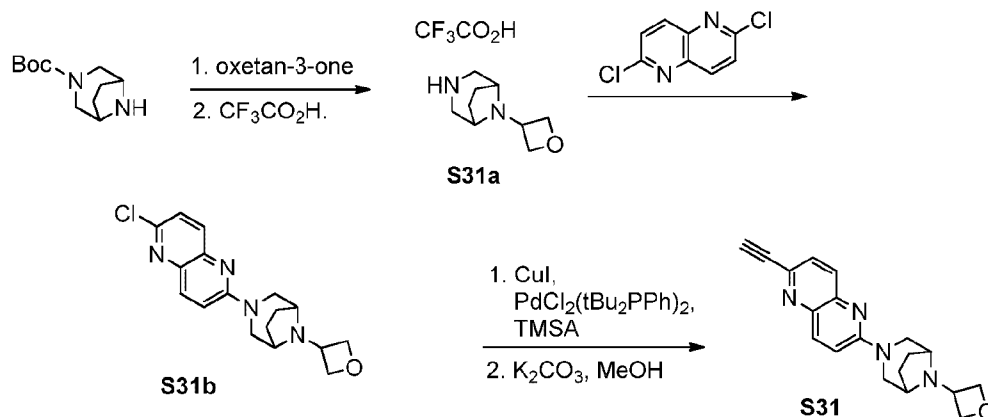
20 Synthesis of (1S,4S)-2-(5-iodopyridin-2-yl)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptane

(S30a) The title compound **S30a** was prepared according to the method presented for the synthesis of compound **S1c** but instead utilizing tert-butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate. MS (ESI) m/z 358.0 $[M+H]^+$.

Synthesis of (1S,4S)-2-(5-ethynylpyridin-2-yl)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]

- 25 **heptane (S30)** The title compound **S30** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S30a**. MS (ESI) m/z 256.2 ($[M+H]^+$). 1H NMR (400 MHz, Chloroform- d) δ 8.12 (dd, J = 2.3, 0.8 Hz, 1H), 7.36 (dd, J = 8.7, 2.3 Hz, 1H), 6.11 (d, J = 8.7 Hz, 1H), 4.59 (s, 1H), 4.53 (dt, J = 12.9, 6.5 Hz, 2H), 4.36 (dt, J = 31.2, 5.3 Hz, 2H),

3.82 (p, J = 5.9 Hz, 1H), 3.44 (s, 1H), 3.17 (s, 1H), 2.91 (s, 1H), 2.87 - 2.73 (m, 1H), 2.75 - 2.64 (m, 1H), 1.94 - 1.78 (m, 1H), 1.73 (d, J = 9.7 Hz, 1H).

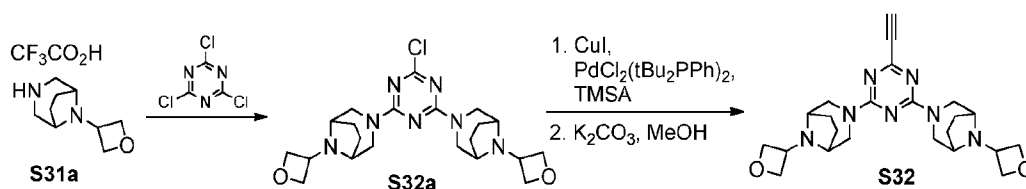


5

Synthesis of 8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octane 2,2,2-trifluoroacetate (S31a). The title compound **S31a** was prepared according to the method presented for the synthesis of compound **S1c** but instead utilizing tert-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate followed by Boc deprotection in the same manner as the synthesis of the compound **S17b**. MS (ESI) m/z 169.2 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 4.79 (t, J = 6.9 Hz, 2H), 4.66 (dd, J = 7.2, 5.2 Hz, 2H), 4.10 (tt, J = 6.8, 5.2 Hz, 1H), 3.76 (dq, J = 5.0, 2.3 Hz, 2H), 3.51 (dd, J = 13.6, 2.0 Hz, 2H), 3.41 - 3.33 (m, 2H), 2.31 - 2.21 (m, 2H), 2.11 - 1.95 (m, 2H).

Synthesis of 2-chloro-6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-1,5-naphthyridine (S31b). The title compound **S31b** was prepared according to the method presented for the synthesis of compound **S1a** but instead utilizing 2,6-dichloro-1,5-naphthyridine. MS (ESI) m/z 330.7 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 7.95 (dd, J = 9.5, 0.8 Hz, 1H), 7.86 (dd, J = 8.8, 0.8 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.07 (d, J = 9.4 Hz, 1H), 4.71 (t, J = 6.2 Hz, 2H), 4.58 (t, J = 5.7 Hz, 2H), 4.05 (d, J = 11.3 Hz, 2H), 3.74 - 3.63 (m, 1H), 3.28 - 3.20 (m, 5H), 1.86 (dd, J = 9.1, 4.4 Hz, 2H).

Synthesis of 2-ethynyl-6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-1,5-naphthyridine (S31). The title compound **S31** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S31b**. MS (ESI) m/z 321.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 7.93 (d, J = 9.5 Hz, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.00 (d, J = 9.5 Hz, 1H), 4.63 (t, J = 6.2 Hz, 2H), 4.50 (t, J = 5.8 Hz, 2H), 4.01 (d, J = 11.8 Hz, 2H), 3.61 (p, J = 6.0 Hz, 1H), 3.27 - 3.07 (m, 4H), 3.06 (s, 1H), 1.77 (dd, J = 8.9, 4.3 Hz, 2H), 1.66 - 1.52 (m, 2H).



Synthesis of 3,3'-(6-chloro-1,3,5-triazine-2,4-diyl)bis(8-(oxetan-3-yl)-3,8-diazabicyclo

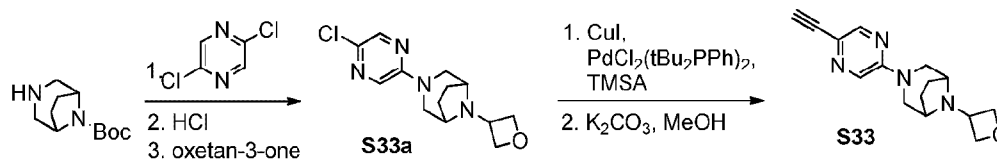
[3.2.1]octane) (**S32a**) The title compound **S32a** was prepared according to the method presented for the synthesis of compound **S1a** but instead utilizing **S31a** and 2,4,6-trichloro-1,3,5-triazine.

- 5 MS (ESI) m/z 448.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 4.70 (t, J = 6.2 Hz, 4H), 4.56 (s, 3H), 4.32 (d, J = 13.0 Hz, 2H), 4.30 - 4.20 (m, 2H), 3.64 (h, J = 5.8 Hz, 2H), 3.21 - 3.04 (m, 8H), 1.89 - 1.73 (m, 4H), 1.71 - 1.51 (m, 5H).

Synthesis of 3,3'-(6-ethynyl-1,3,5-triazine-2,4-diyl)bis(8-(oxetan-3-yl)-3,8-diazabicyclo

[3.2.1]octane) (**S32**). The title compound **S32** was prepared according to the method presented

- 10 for the synthesis of compound **S1** but instead utilizing **S32a**. MS (ESI) m/z 438.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 4.55 (t, J = 6.2 Hz, 4H), 4.48 - 4.33 (m, 4H), 4.23 (d, J = 12.5 Hz, 2H), 4.12 (t, J = 10.9 Hz, 2H), 3.49 (q, J = 5.7 Hz, 2H), 3.05 - 2.85 (m, 8H), 2.78 (s, 1H), 1.71 - 1.57 (m, 4H), 1.52 - 1.34 (m, 4H).



Synthesis of 3-(5-chloropyrazin-2-yl)-8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octane (**S33a**)

The title compound **S33a** was prepared according to the method presented for the synthesis of compound **S1c** but instead utilizing 2,5-dichloropyrazine MS (ESI) m/z 281.3 [M+H]⁺. ¹H

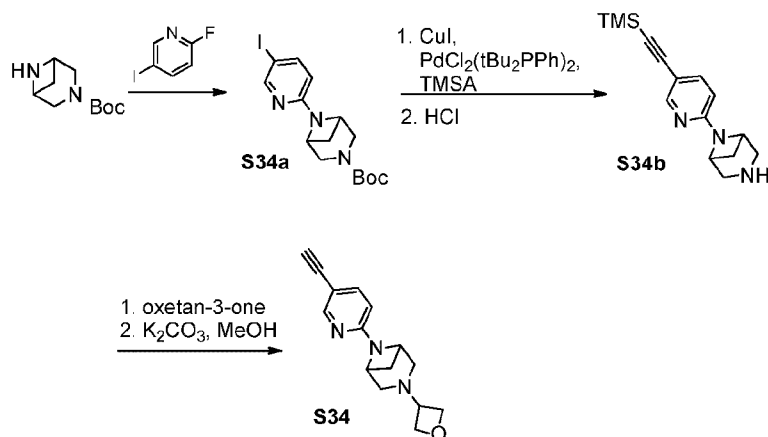
- 20 NMR (400 MHz, Chloroform-d) δ 8.04 (d, J = 1.4 Hz, 1H), 7.74 (d, J = 1.5 Hz, 1H), 4.72 (t, J = 6.3 Hz, 2H), 4.58 (t, J = 5.8 Hz, 2H), 3.77 (dd, J = 11.6, 2.3 Hz, 2H), 3.69 (ddd, J = 11.9, 6.5, 5.5 Hz, 1H), 3.23 (dd, J = 4.8, 2.6 Hz, 2H), 3.18 (dd, J = 11.5, 2.3 Hz, 2H), 1.92 - 1.83 (m, 2H), 1.73 - 1.65 (m, 2H).

Synthesis of 3-(5-ethynylpyrazin-2-yl)-8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octane (**S33**)

- 25 The title compound **S33** was prepared according to the method presented for the synthesis of

compound **S1** but instead utilizing **S33a**. MS (ESI) m/z 271.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 8.21 (d, J = 1.5 Hz, 1H), 7.98 (d, J = 1.5 Hz, 1H), 4.73 (dd, J = 6.3 Hz, 2H), 4.59 (t, J = 5.8 Hz, 2H), 3.90 (d, J = 10.5 Hz, 1H), 3.70 (p, J = 6.0 Hz, 1H), 3.27 - 3.18 (m, 4H),

3.17 (s, 1H), 1.94 - 1.83 (m, 2H), 1.74 - 1.64 (m, 2H), 1.57 (s, 1H).



Synthesis of tert-butyl 6-(5-iodopyridin-2-yl)-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate

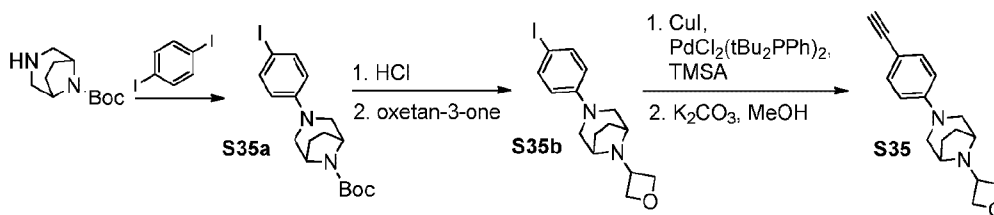
- 5 (S34a) The title compound **S34a** was prepared according to the method presented for the synthesis of compound **S1a** but instead utilizing tert-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate. MS (ESI) m/z 401.8 $[M+H]^+$.

Synthesis of 6-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)-3,6-diazabicyclo[3.1.1]heptane

- (S34b). The title compound **S34b** was prepared according to the method presented for the synthesis of compound **S1c** but instead utilizing **S34a**. MS (ESI) m/z 272.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.22 - 8.09 (m, 1H), 8.01 (d, J = 1.9 Hz, 1H), 7.93 (d, J = 1.6 Hz, 1H), 7.78 (d, J = 8.7 Hz, 1H), 6.97 (d, J = 9.2 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 5.87 (d, J = 2.8 Hz, 1H), 5.47 (d, J = 2.7 Hz, 1H), 4.86 - 4.71 (m, 3H), 3.69 - 3.57 (m, 3H), 3.53 - 3.44 (m, 3H), 3.10 - 3.03 (m, 3H), 2.96 (d, J = 9.0 Hz, 2H), 2.02 - 1.95 (m, 1H), 0.00 (s, 9H).

- 15 **Synthesis of 6-(5-ethynylpyridin-2-yl)-3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptane (S34).**

- The title compound **S34** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S34b**. MS (ESI) m/z 256.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.32 (d, J = 2.1 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 6.26 (d, J = 8.6 Hz, 1H), 4.56 (t, J = 6.8 Hz, 2H), 4.51 - 4.32 (m, 4H), 3.73 (s, 1H), 3.26 - 3.11 (m, 2H), 3.08 (s, 1H), 3.00 - 2.85 (m, 2H), 2.71 - 2.58 (m, 1H), 2.21 - 1.98 (m, 1H).

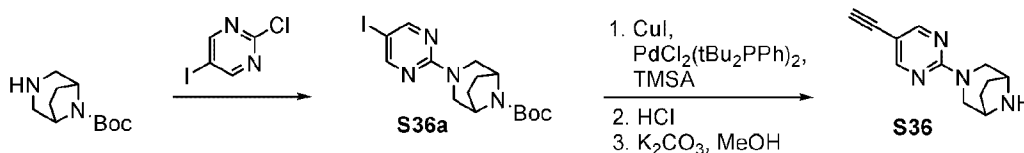


Synthesis of tert-butyl 3-(4-iodophenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (S35a).

The title compound **S35a** was prepared according to the method presented for the synthesis of compound **S1c** but instead utilizing 1,4-diiodobenzene. MS (ESI) m/z 414.9 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 7.56 - 7.43 (m, 2H), 6.68 - 6.55 (m, 2H), 4.34 (s, 2H), 3.35 (dd, J = 11.2, 2.4 Hz, 2H), 2.97 (s, 2H), 2.00 - 1.80 (m, 4H), 1.46 (s, 9H).

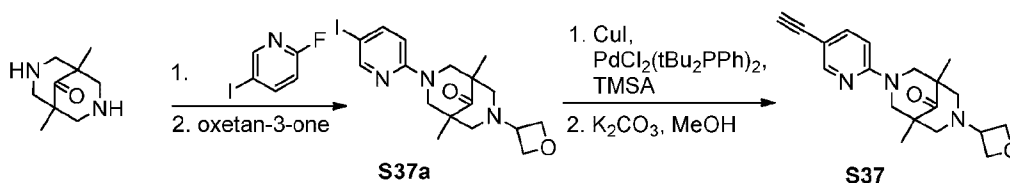
Synthesis of 3-(4-iodophenyl)-8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octane (S35b). The title compound **S35b** was prepared according to the method presented for the synthesis of compound **S1c** but instead utilizing **S35a**. MS (ESI) m/z 371.2 $[M+H]^+$.

Synthesis of 3-(4-ethynylphenyl)-8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octane (S35). The title compound **S35** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S35b**. MS (ESI) m/z 269.2 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 7.19 - 7.08 (m, 2H), 6.53 - 6.40 (m, 2H), 4.49 (t, J = 6.3 Hz, 2H), 4.36 (s, 2H), 3.50 (s, 1H), 3.18 (dd, J = 11.0, 2.5 Hz, 2H), 3.00 (s, 2H), 2.84 (d, J = 10.7 Hz, 2H), 2.75 (s, 1H), 1.72 - 1.47 (m, 4H).



Synthesis of tert-butyl 3-(5-iodopyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (S36a). The title compound **S36a** was prepared according to the method presented for the synthesis of compound **S1a** but instead utilizing 2-chloro-5-iodopyrimidine. MS (ESI) m/z 416.8 $[M+H]^+$.

Synthesis of 3-(5-ethynylpyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane (S36). The title compound **S36** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S36a**. MS (ESI) m/z 215.2 $[M+H]^+$.



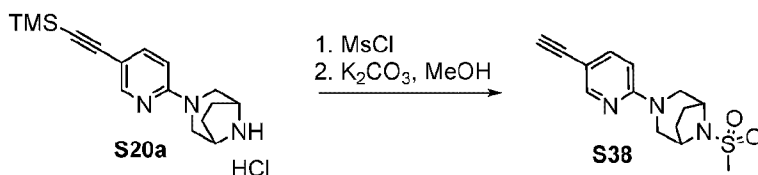
Synthesis of 3-(5-iodopyridin-2-yl)-1,5-dimethyl-7-(oxetan-3-yl)-3,7-diazabicyclo[3.3.1]

nonan-9-one (S37a). The title compound **S37a** was prepared according to the method presented for the synthesis of compound **S1c** but instead utilizing 1,5-dimethyl-3,7-

- 5 diazabicyclo[3.3.1]nonan-9-one. MS (ESI) m/z 428.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.34 (s, 1H), 7.71 (s, 1H), 6.62 (s, 1H), 4.70 (s, 2H), 4.37 (t, J = 6.5 Hz, 2H), 4.15 (t, J = 6.4 Hz, 3H), 3.29 - 3.05 (m, 3H), 3.02 - 2.80 (m, 1H), 2.17 (dd, J = 11.2, 2.3 Hz, 2H), 1.55 (s, 2H), 1.03 (s, 6H).

Synthesis of 3-(5-ethynylpyridin-2-yl)-1,5-dimethyl-7-(oxetan-3-yl)-3,7-diazabicyclo[3.3.1]

- 10 **nonan-9-one (S37)** The title compound **S37** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S37a**. MS (ESI) m/z 326.3 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.34 (d, J = 2.2 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 6.69 (d, J = 8.9 Hz, 1H), 4.80 (d, J = 13.4 Hz, 2H), 4.34 (t, J = 6.4 Hz, 2H), 4.12 (t, J = 6.2 Hz, 2H), 3.24 - 2.99 (m, 3H), 2.91 (d, J = 10.9 Hz, 2H), 2.17 (dd, J = 11.3, 2.3 Hz, 2H), 1.55 (s, 1H), 1.03 (s,
- 15 6H).

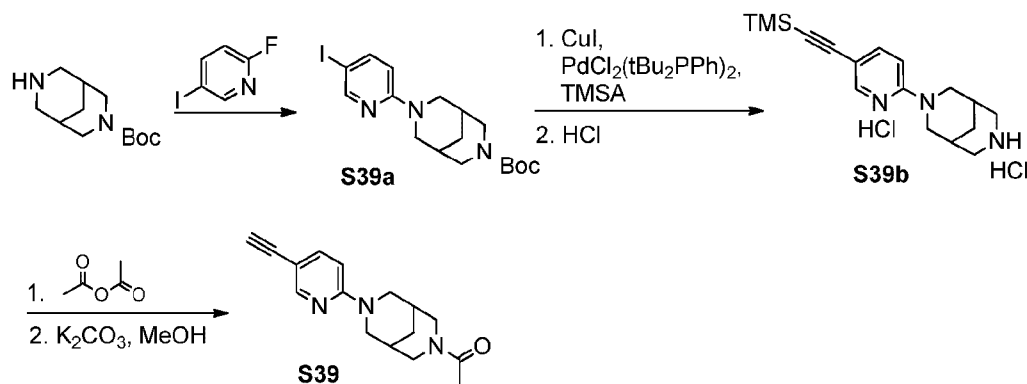


Synthesis of 3-(5-ethynylpyridin-2-yl)-8-(methylsulfonyl)-3,8-diazabicyclo[3.2.1]octane

(S38). To a solution of **S20a** (630 mg, 1.76 mmol) in DCM (10mL) was added *N,N*-

- 20 diisopropylethylamine (1.22 ml, 0.01 mol), the mixture was cooled to 5°C, and then methanesulfonyl chloride (0.2 ml, 3.0 mmol) was added. After 3 min the reaction was quenched with $NaHCO_3$ saturated solution, the organic layer was separated, dried over Na_2SO_4 , filtered, concentrated and the residue was dissolved in MeOH (15 mL), the solution was cooled to 10°C, then added K_2CO_3 (0.44 g, 0.01 mol). After 15 min the precipitate was filtered off, rinsed with
- 25 10% MeOH in water and dried under vacuum to give **S38** (477 mg, 93.1%) MS (ESI) m/z 292.2 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.07 (dd, J = 2.3, 0.8 Hz, 1H), 7.32 (dd, J = 8.8, 2.3 Hz, 1H), 6.26 (d, J = 8.8 Hz, 1H), 4.12 (dd, J = 4.7, 2.4 Hz, 2H), 3.83 (dd, J = 12.3, 2.5 Hz,

2H), 2.92 (dd, $J = 12.1, 2.1$ Hz, 2H), 2.84 (s, 1H), 2.75 (s, 3H), 1.89 - 1.76 (m, 2H), 1.65 - 1.56 (m, 2H).



Synthesis of tert-butyl 7-(5-iodopyridin-2-yl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

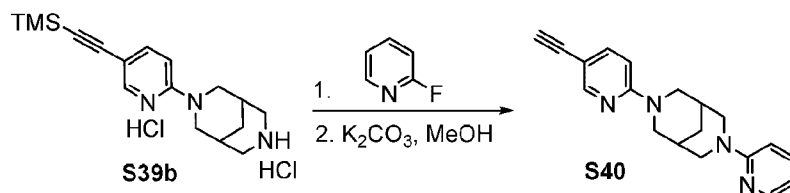
- 5 (S39a). The title compound **S39a** was prepared according to the method presented for the synthesis of compound **S1a** but instead utilizing tert-butyl 3,7-diazabicyclo[3.3.1]nonane-3-carboxylate. MS (ESI) m/z 430.2 $[\text{M}+\text{H}]^+$.

Synthesis of 3-(5-((trimethylsilyl)ethynyl)pyridin-2-yl)-3,7-diazabicyclo[3.3.1]nonane dihydrochloride (S39b).

- 10 presented for the synthesis of compound **S1** but instead utilizing **S39a**. MS (ESI) m/z 300.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Methanol- d_4) δ 7.97 (d, $J = 2.2$ Hz, 1H), 7.74 (dd, $J = 9.4, 2.2$ Hz, 1H), 7.10 (d, $J = 9.3$ Hz, 1H), 4.00 (d, $J = 12.6$ Hz, 2H), 3.30 (d, $J = 13.0$ Hz, 2H), 3.21 (t, $J = 11.5$ Hz, 2H), 3.12 (d, $J = 13.0$ Hz, 2H), 2.21 (s, 2H), 1.87 (d, $J = 13.8$ Hz, 1H), 1.78 (d, $J = 13.7$ Hz, 1H), 0.00 (s, 9H).

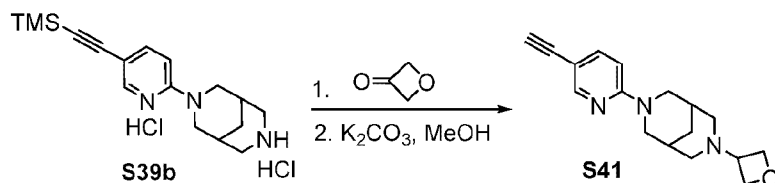
- 15 **Synthesis of 1-(7-(5-ethynylpyridin-2-yl)-3,7-diazabicyclo[3.3.1]nonan-3-yl)ethan-1-one (S39).** To a mixture of **S39b** (0.39 g, 1 mmol) and Et_3N (0.73 mL, 0.01 mol) in DCM (10 mL), acetic anhydride (0.14 mL, 1 mmol) was added. After 5 min, the reaction was quenched with 1M NaOH, the layers were separated and the organic layer was dried over Na_2SO_4 , filtered, concentrated and the residue was dissolved in MeOH (20 mL), then added K_2CO_3 (0.44 g, 3 mmol). After 20 min the reaction was diluted with DCM, washed with water, the organic layer was dried over Na_2SO_4 , filtered, concentrated under reduced pressure and the residue was purified by silica column chromatography (60% - 100% EtOAc/hexanes to 5% MeOH / EtOAc) to give **S39** (111 mg, 39%) MS (ESI) m/z 270.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Methanol- d_4) δ 8.12 (dd, $J = 2.3, 0.8$ Hz, 1H), 7.48 (dd, $J = 9.0, 2.4$ Hz, 1H), 6.69 (dd, $J = 9.0, 0.8$ Hz, 1H), 4.74 - 4.59 (m, 2H), 4.33 - 4.20 (m, 1H), 4.04 (d, $J = 13.4$ Hz, 1H), 3.42 (dt, $J = 13.5, 2.7$ Hz, 1H), 3.39 (s, 1H), 3.11 (dddd, $J = 11.1, 8.0, 3.2, 2.2$ Hz, 2H), 2.87 (dt, $J = 13.5, 2.6$ Hz, 1H), 2.06 (q, J
- 25

= 3.0 Hz, 2H), 2.01 - 1.94 (m, 2H), 1.84 (s, 3H).



Synthesis of 3-(5-ethynylpyridin-2-yl)-7-(pyridin-2-yl)-3,7-diazabicyclo[3.3.1]nonane (S40).

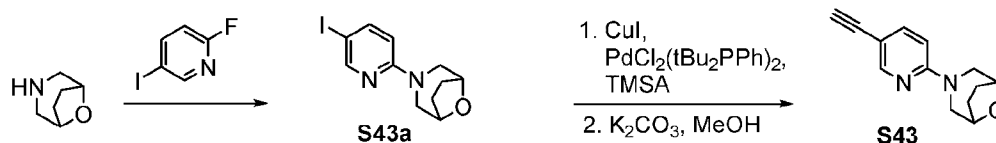
- 5 In a microwave tube a mixture of S39b (0.21 g, 0.6 mmol), 2-Fluoropyridine (0.1 ml, 1 mmol), sodium bicarbonate (0.24 g, 3 mol) in NMP (1 mL) were microwaved at 130°C for 20 min, then at 150°C for 20 min, the reaction was diluted with DCM, washed with water, the organic layer was dried over Na₂SO₄, filtered, concentrated under reduced pressure and the residue was purified by silica column chromatography to give **S40** (9 mg, 5%) MS (ESI) m/z 305.2 [M+H]⁺.
- 10 ¹H NMR (400 MHz, Chloroform-d) δ 8.06 (d, J = 2.3 Hz, 1H), 7.93 (dd, J = 5.1, 2.0 Hz, 1H), 7.25 (dd, J = 9.0, 2.4 Hz, 1H), 7.25 - 7.16 (m, 1H), 6.39 (d, J = 8.7 Hz, 1H), 6.36 - 6.30 (m, 2H), 4.39 - 4.17 (m, 4H), 3.15 - 3.02 (m, 5H), 2.93 (s, 1H), 2.18 - 2.07 (m, 2H), 1.89 (d, J = 3.4 Hz, 2H).



- 15 **Synthesis of 3-(5-ethynylpyridin-2-yl)-7-(oxetan-3-yl)-3,7-diazabicyclo[3.3.1]nonane (S41).**

The title compound **S41** was prepared according to the method presented for the synthesis of compound **S1c** but instead utilizing **S39b**. MS (ESI) m/z 284.3 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.17 - 7.96 (m, 1H), 7.46 (dd, J = 9.0, 2.4 Hz, 1H), 6.77 - 6.49 (m, 1H), 4.41 (t, J = 6.4 Hz, 2H), 4.26 (t, J = 6.2 Hz, 2H), 4.19 (d, J = 12.9 Hz, 2H), 3.31 (s, 1H), 3.23 - 3.12 (m, 3H), 2.80 - 2.65 (m, 2H), 2.13 - 1.91 (m, 4H), 1.91 - 1.76 (m, 1H), 1.73 - 1.61 (m, 1H).

20



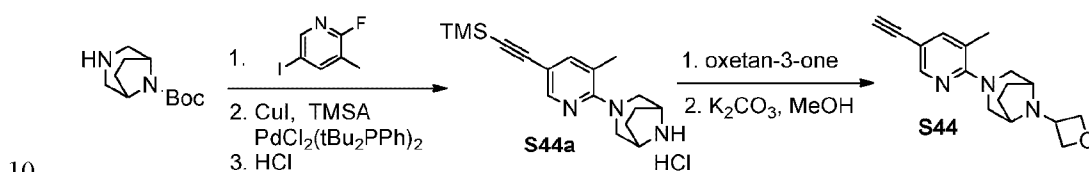
- 25 **Synthesis of 3-(5-iodopyridin-2-yl)-8-oxa-3-azabicyclo[3.2.1]octane (S43a).** The title

compound **S43a** was prepared according to the method presented for the synthesis of compound **S1a** but instead utilizing 8-oxa-3-azabicyclo[3.2.1]octane. MS (ESI) m/z 317.1 $[M+H]^+$.

Synthesis of 3-(5-ethynylpyridin-2-yl)-8-oxa-3-azabicyclo[3.2.1]octane (S43b). The title

compound **S43** was prepared according to the method presented for the synthesis of compound

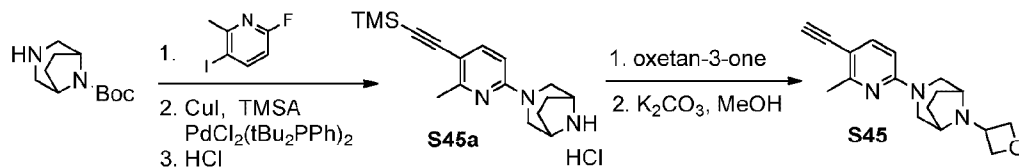
- 5 **S1** but instead utilizing **S43a**. MS (ESI) m/z 215.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.17 (dd, J = 2.3, 0.8 Hz, 1H), 7.56 (dd, J = 8.9, 2.3 Hz, 1H), 6.67 (dd, J = 8.9, 0.8 Hz, 1H), 4.46 (dq, J = 4.4, 2.3 Hz, 2H), 3.86 (dt, J = 12.8, 1.1 Hz, 2H), 3.43 (s, 1H), 3.07 (d, J = 2.6 Hz, 1H), 3.03 (d, J = 2.6 Hz, 1H), 2.02 - 1.74 (m, 4H).



Synthesis of 3-(3-methyl-5-((trimethylsilyl)ethynyl)pyridin-2-yl)-3,8-diazabicyclo[3.2.1]

octane (S44a) The title compound **S44a** was prepared according to the methods presented for the synthesis of compound **S3** but instead utilizing 2-fluoro-5-iodo-3-methylpyridine. MS (ESI) m/z 300.3 $[M+H]^+$.

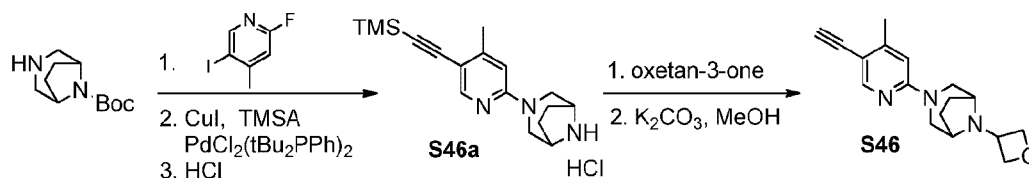
- 15 **Synthesis of 3-(5-ethynyl-3-methylpyridin-2-yl)-8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octane (S44).** The title compound **S44** was prepared according to the methods presented for the synthesis of compound **S3** but instead utilizing **S44a**. MS (ESI) m/z 284.2 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.24 (d, J = 2.2 Hz, 1H), 8.05 (d, J = 2.3 Hz, 0H), 7.43 (dd, J = 2.1, 0.9 Hz, 1H), 7.30 (d, J = 1.9 Hz, 0H), 7.19 (d, J = 15.2 Hz, 0H), 5.80 (d, J = 15.1 Hz, 0H), 5.30 (s, 0H), 4.70 (t, J = 6.2 Hz, 3H), 4.59 (s, 2H), 3.76 (s, 1H), 3.35 - 3.26 (m, 2H), 3.18 (d, J = 30.6 Hz, 5H), 3.09 (s, 1H), 2.27 (s, 0H), 2.24 (s, 3H), 1.96 - 1.79 (m, 5H), 0.24 (d, J = 7.3 Hz, 0H), 0.15 (d, J = 6.0 Hz, 0H), 0.08 (s, 0H).
- 20



- 25 **Synthesis of 3-(6-methyl-5-((trimethylsilyl)ethynyl)pyridin-2-yl)-3,8-diazabicyclo[3.2.1]octane (S45a)** The title compound **S45a** was prepared according to the methods presented for the synthesis of compound **S3** but instead utilizing 6-fluoro-3-iodo-2-methylpyridine. MS (ESI) m/z 300.3 $[M+H]^+$.

Synthesis of 3-(5-ethynyl-6-methylpyridin-2-yl)-8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]

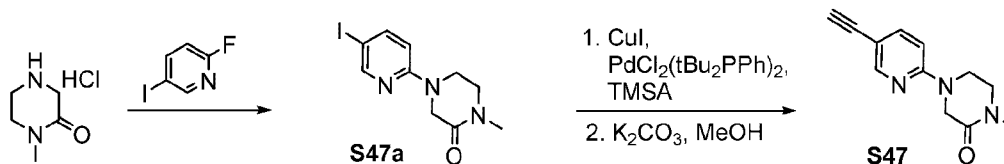
octane (S45). The title compound **S45** was prepared according to the methods presented for the synthesis of compound **S3** but instead utilizing **S45a**. MS (ESI) m/z 284.2 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 7.46 (d, J = 8.7 Hz, 1H), 6.28 (d, J = 8.7 Hz, 1H), 5.30 (s, 0H), 4.72 (t, J = 6.3 Hz, 2H), 4.59 (t, J = 5.8 Hz, 2H), 4.07 (d, J = 12.6 Hz, 0H), 3.89 (d, J = 11.0 Hz, 2H), 3.71 (p, J = 6.0 Hz, 1H), 3.26 (d, J = 13.4 Hz, 1H), 3.24 (s, 0H), 3.23 (s, 1H), 3.19 (s, 2H), 3.14 - 3.07 (m, 2H), 2.51 (s, 3H), 1.85 (dd, J = 11.5, 6.7 Hz, 2H), 1.70 (t, J = 6.7 Hz, 1H).

**Synthesis of 3-(4-methyl-5-((trimethylsilyl)ethynyl)pyridin-2-yl)-3,8-diazabicyclo[3.2.1]**

octane (S46a) The title compound **S46a** was prepared according to the methods presented for the synthesis of compound **S3** but instead utilizing 2-fluoro-5-iodo-4-methylpyridine. MS (ESI) m/z 300.4 $[M+H]^+$.

Synthesis of 3-(5-ethynyl-4-methylpyridin-2-yl)-8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]

octane (S46). The title compound **S46** was prepared according to the methods presented for the synthesis of compound **S3** but instead utilizing **S46a**. MS (ESI) m/z 284.2 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.22 (s, 1H), 6.33 (s, 1H), 5.30 (s, 0H), 4.72 (t, J = 6.3 Hz, 2H), 4.59 (t, J = 5.8 Hz, 2H), 3.85 (dd, J = 11.8, 2.4 Hz, 2H), 3.70 (p, J = 6.0 Hz, 1H), 3.24 (s, 0H), 3.23 (s, 1H), 3.22 - 3.09 (m, 4H), 2.34 (d, J = 0.7 Hz, 3H), 1.85 (dd, J = 8.9, 4.3 Hz, 2H), 1.72 - 1.66 (m, 2H).

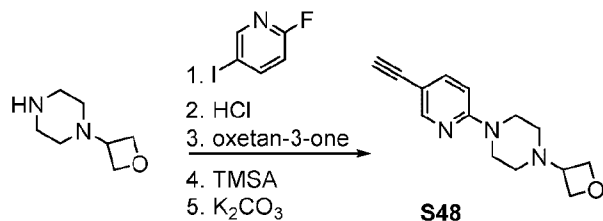
**Synthesis of 4-(5-iodopyridin-2-yl)-1-methylpiperazin-2-one (S47a).**

The title compound **S47a** was prepared according to the methods presented for the synthesis of compound **S1a** but instead utilizing 1-Methylpiperazin-2-one hydrochloride. MS (ESI) m/z 318.0 $[M+H]^+$.

Synthesis of 3-(5-ethynyl-4-methylpyridin-2-yl)-8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]

octane 4-(5-ethynylpyridin-2-yl)-1-methylpiperazin-2-one (S47). The title compound **S47**

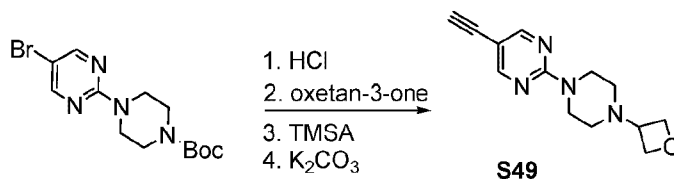
was prepared according to the methods presented for the synthesis of compound **S3** but instead utilizing **S47a**. MS (ESI) m/z 216.1 $[M+H]^+$.



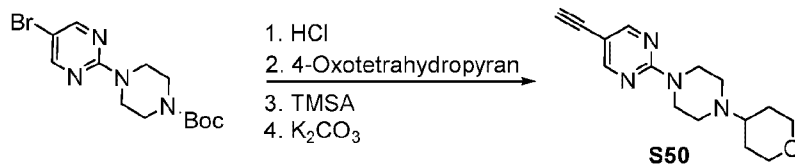
5

Synthesis of 1-(5-ethynylpyridin-2-yl)-4-(oxetan-3-yl)piperazine (S48). The title compound **S48** was prepared according to the methods presented for the synthesis of compound **S1** but instead utilizing 1-(oxetan-3-yl) piperazine. MS (ESI) m/z 244.16 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.18 (d, J = 2.2 Hz, 1H), 7.56 (dd, J = 8.9, 2.3 Hz, 1H), 6.75 (d, J = 8.9 Hz, 1H), 4.70 (t, J = 6.6 Hz, 3H), 4.63 (t, J = 6.2 Hz, 3H), 3.68 - 3.56 (m, 6H), 3.55 - 3.47 (m, 1H), 3.42 (s, 1H), 2.52 - 2.37 (m, 6H), 1.27 (d, J = 13.9 Hz, 0H).

10



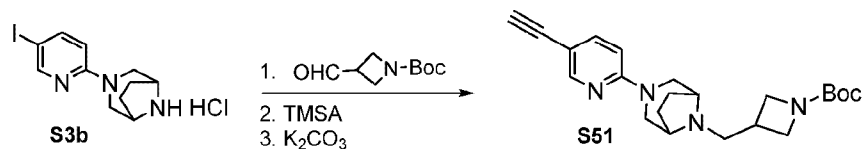
Synthesis of 5-ethynyl-2-(4-(oxetan-3-yl)piperazin-1-yl)pyrimidine (S49). The title compound **S49** was prepared according to the methods presented for the synthesis of compound **S1** but instead utilizing tert-butyl 4-(5-bromopyrimidin-2-yl)piperazine-1-carboxylate. MS (ESI) m/z 245.2 $[M+H]^+$.



20

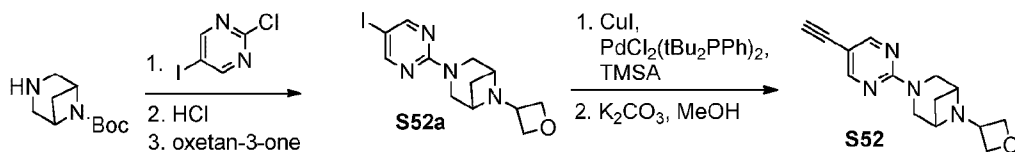
Synthesis of 5-ethynyl-2-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)pyrimidine (S50).

The title compound **S50** was prepared according to the methods presented for the synthesis of compound **S1** but instead utilizing tert-butyl 4-(5-bromopyrimidin-2-yl)piperazine-1-carboxylate and 4-Oxotetrahydropyran. MS (ESI) m/z 272.70 $[M+H]^+$.



Synthesis of tert-butyl 3-((3-(5-ethynylpyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-

- 5 **yl)methyl)azetidine-1-carboxylate (S51).** The title compound **S51** was prepared according to the methods presented for the synthesis of compound **S1** but instead utilizing **S3b** and tert-butyl 3-formylazetidine-1-carboxylate. MS (ESI) m/z 383.05 $[\text{M}+\text{H}]^+$.

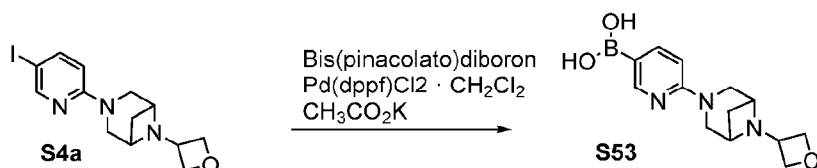


- 10 **Synthesis of 3-(5-iodopyrimidin-2-yl)-6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptane (S52a)**

The title compound **S52a** was prepared according to the method presented for the synthesis of compound **S1c** but instead utilizing tert-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate and 2-chloro-5-iodopyrimidine. MS (ESI) m/z 359.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.47 (s, 2H), 4.70 (t, J = 6.2 Hz, 2H), 4.48 (t, J = 5.5 Hz, 2H), 3.87 (p, J = 5.5 Hz, 1H), 3.81 (d, J = 6.1 Hz, 2H), 3.56 (q, J = 13.2 Hz, 4H), 2.74 (q, J = 7.8 Hz, 1H), 1.58 (d, J = 8.9 Hz, 1H).

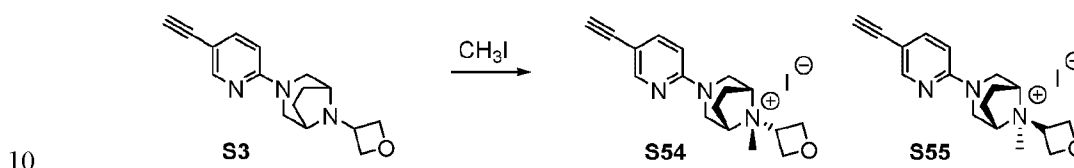
15 **Synthesis of 3-(5-ethynylpyrimidin-2-yl)-6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptane (S52)**

The title compound **S52** was prepared according to the method presented for the synthesis of compound **S1** but instead utilizing **S52a**. MS (ESI) m/z 257.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.32 (s, 2H), 4.55 (t, J = 6.1 Hz, 2H), 4.32 (dd, J = 6.0, 4.8 Hz, 2H), 3.72 (ddd, J = 11.1, 6.2, 4.9 Hz, 1H), 3.65 (d, J = 6.0 Hz, 2H), 3.50 (d, J = 13.3 Hz, 2H), 3.43 (d, J = 13.3 Hz, 2H), 3.06 (s, 1H), 2.58 (dt, J = 8.1, 6.1 Hz, 1H), 1.44 (d, J = 8.8 Hz, 1H).



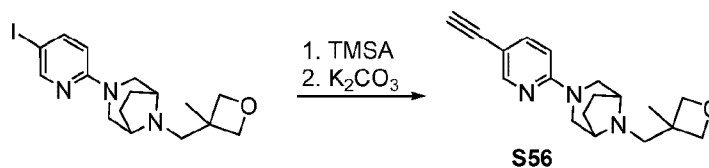
- 25 **Synthesis of (6-(6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)boronic acid (S53)** A suspension of **S4a** (0.17 g, 0.47 mmol) Bis (Pinacolato) Diboron (0.18 g, 0.72

mmol), potassium acetate (0.17 g, 1.68 mmol) and [1,1' bis(diphenylphosphino)ferrocene] dichloropalladium (II) (0.04 g, 0.05 mmol) in DMF (4.5 mL) was degassed with argon for 5 min, then heated at 90 °C for 1 h. Cooled to room temperature, Diluted with EtOAc and washed with 5% LiCl solution 2x. The separated organic layer was dried over Na₂SO₄ and concentrated under vacuum, the residue was purified by HPLC and the product was lyophilized to afford S53. MS (ESI) m/z 276.2 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.35 (d, J = 1.7 Hz, 1H), 8.31 (dd, J = 9.0, 1.8 Hz, 1H), 7.18 (d, J = 9.0 Hz, 1H), 4.74 - 4.58 (m, 4H), 4.27 - 3.99 (m, 4H), 3.28 - 3.16 (m, 1H), 2.21 - 2.06 (m, 2H).



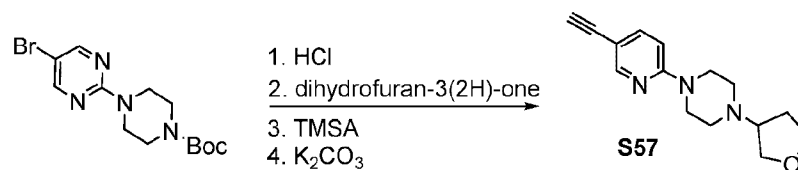
Synthesis of 3-(5-ethynylpyridin-2-yl)-8-methyl-8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-8-ium iodide (S54 and S55).

To a solution of S3 in acetone (1 mL) in a vial at 30 °C was added Iodomethane (0.06 ml, 1.0 mmol), warmed up to 70 °C and the mixture was stirred overnight. After cooling to room temperature the reaction was diluted with ether, stirred for 5 min, the solids were filtered and dried in vacuum to afford a 3:1 mixture of isomers (S54 : S55) where the major product (S4) has the methyl syn to the bridge. MS (ESI) m/z 284.0 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.08 - 8.02 (m, 1H), 7.50 - 7.40 (m, 1H), 6.58 (d, J = 9.0 Hz, 0H), 6.54 (dd, J = 8.8, 0.9 Hz, 1H), 5.37 (t, J = 8.1 Hz, 1H), 4.86 - 4.70 (m, 5H), 4.05 - 3.94 (m, 3H), 3.88 (d, J = 14.3 Hz, 3H), 3.54 (d, J = 14.7 Hz, 1H), 3.45 (s, 1H), 3.37 (d, J = 2.1 Hz, 1H), 3.34 (s, 4H), 3.30 (s, 1H), 2.37 - 2.27 (m, 2H), 2.21 - 2.11 (m, 1H), 2.07 - 1.94 (m, 2H), 1.94 (s, 1H).

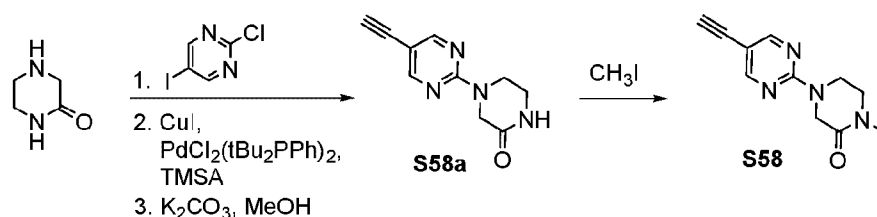


Synthesis of 3-(5-ethynylpyridin-2-yl)-8-((3-methyloxetan-3-yl)methyl)-3,8-

25 **diazabicyclo[3.2.1]octane (S56).** The title compound S56 was prepared according to the methods presented for the synthesis of compound S1 but instead utilizing 3-(5-iodopyridin-2-yl)-8-((3-methyloxetan-3-yl)methyl)-3,8-diazabicyclo[3.2.1]octane. MS (ESI) m/z 298.19 [M+H]⁺.

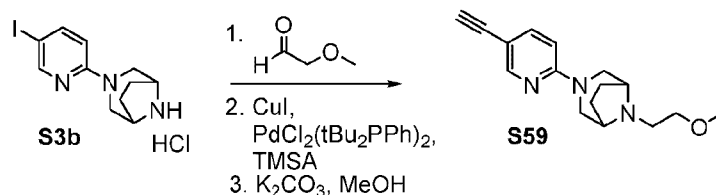


Synthesis of 1-(5-ethynylpyridin-2-yl)-4-(tetrahydrofuran-3-yl)piperazine (S57). The title compound **S57** was prepared according to the methods presented for the synthesis of compound **S50** but instead utilizing dihydrofuran-3(2H)-one. ¹H-NMR and MS data identical to S14.



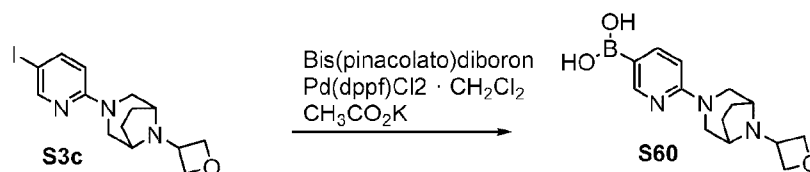
Synthesis of 4-(5-ethynylpyrimidin-2-yl)piperazin-2-one (S58a). The title compound **S58a** was prepared according to the methods presented for the synthesis of compound **S47** but instead utilizing piperazin-2-one and 2-chloro-5-iodopyrimidine MS (ESI) m/z 303.0 $[\text{M}+\text{H}]^+$. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.44 (s, 2H), 6.11 (s, 1H), 4.46 (s, 2H), 4.16 - 3.91 (m, 2H), 3.47 (td, J = 5.4, 2.7 Hz, 2H), 3.19 (s, 1H).

Synthesis of 4-(5-ethynylpyrimidin-2-yl)-1-methylpiperazin-2-one (S58). To a solution of **S58a** (115 mg, 0.57 mmol) in THF (5 mL) and DMF (1 mL) at 0 °C was added sodium hydride, (60% oil dispersion, 59 mg, 1.475 mmol). After 15 min, added iodomethane (0.15 ml, 2.409 mmol). The reaction mixture was warmed up to room temperature and stirred for 2 h, then quenched with water and partitioned with EtOAc. The separated organic layer was dried over Na_2SO_4 and concentrated under vacuum to afford **S58** (124.9 mg, 100%). MS (ESI) m/z 217.1 $[\text{M}+\text{H}]^+$. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.45 (s, 2H), 4.37 (s, 2H), 4.18 - 4.03 (m, 2H), 3.65 (s, 1H), 3.57 - 3.43 (m, 2H), 3.01 (s, 3H).

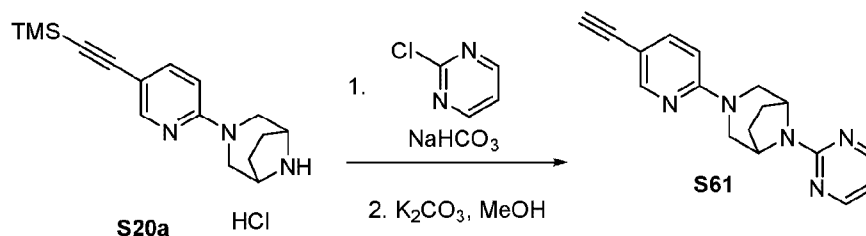


Synthesis of 3-(5-ethynylpyridin-2-yl)-8-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octane

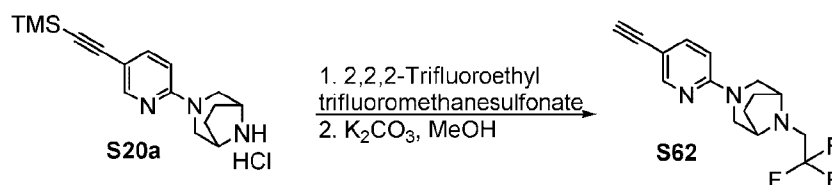
(S59). The title compound **S59** was prepared according to the methods presented for the synthesis of compound **S3** but instead utilizing 2-methoxyacetaldehyde. MS (ESI) m/z 303.02 $[M+H]^+$.



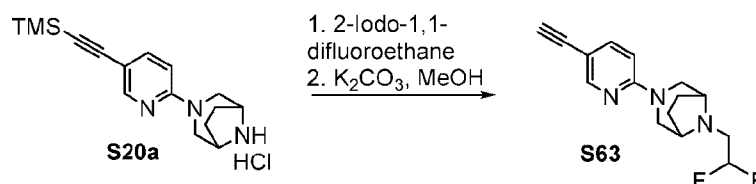
- 5 **Synthesis of (6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)boronic acid (S60).** The title compound **S60** was prepared according to the methods presented for the synthesis of compound **S53** but instead utilizing **S3c**. MS (ESI) m/z 290.2 $[M+H]^+$. ^1H NMR (400 MHz, Methanol- d_4) δ 8.33 (s, 1H), 8.08 (d, $J = 9.2$ Hz, 1H), 7.04 (d, $J = 8.9$ Hz, 1H), 4.91 (t, $J = 7.3$ Hz, 3H), 4.76 (dd, $J = 7.7, 5.2$ Hz, 2H), 4.36 (s, 1H), 4.17 (d, $J = 13.4$ Hz, 3H), 4.00 (s, 2H), 3.46 (d, $J = 13.2$ Hz, 2H), 2.28 - 2.10 (m, 2H), 2.01 (d, $J = 8.4$ Hz, 2H).
- 10



- Synthesis of 3-(5-ethynylpyridin-2-yl)-8-(pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane (S61).** A suspension of **S20a** (0.15 g, 0.42 mmol), sodium bicarbonate (250 mg, 2.9 mmol), and 2-Chloropyrimidine (0.17 g, 1.5 mmol) in isopropanol (1.5 mL) was stirred at 65 °C overnight.
- 15 The reaction mixture was then cooled to room temperature, diluted with ethyl acetate and filtered through celite. The crude mixture was concentrated *in vacuo* and redissolved in methanol (5 mL). Potassium carbonate (0.29 g, 2.1 mmol) was added and the mixture was stirred for 30 minutes. The reaction was quenched with water and the crude product was extracted into DCM, dried over sodium sulfate, filtered, concentrated *in vacuo*, and purified by
- 20 column chromatography (30% $\rightarrow$ 70% EtOAc $\rightarrow$ hexanes). MS (ESI) m/z 292.2 $[M+H]^+$. ^1H NMR (400 MHz, Methanol- d_4) δ 8.35 (d, $J = 4.8$ Hz, 2H), 8.17 (dd, $J = 2.4, 0.8$ Hz, 1H), 7.55 (dd, $J = 8.9, 2.3$ Hz, 1H), 6.69 (dd, $J = 9.0, 0.8$ Hz, 1H), 6.64 (t, $J = 4.8$ Hz, 1H), 4.89 (dq, $J = 4.6, 2.3$ Hz, 3H), 4.02 (dd, $J = 12.4, 2.3$ Hz, 3H), 3.42 (s, 1H), 3.13 (dd, $J = 12.3, 2.3$ Hz, 3H), 2.08 - 1.96 (m, 3H), 1.96 - 1.82 (m, 3H).

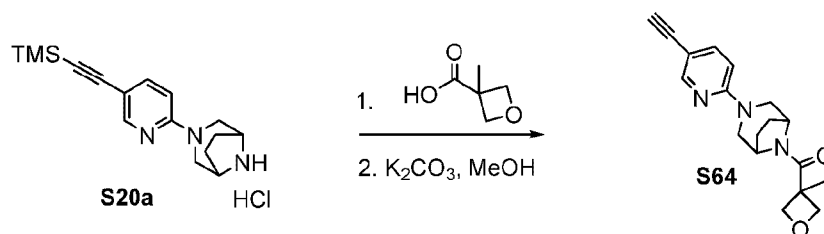


3-(5-ethynylpyridin-2-yl)-8-(2,2,2-trifluoroethyl)-3,8-diazabicyclo[3.2.1]octane (S62). The title compound **S62** was prepared according to the methods presented for the synthesis of compound **S63** but instead utilizing 2,2,2-Trifluoroethyl trifluoromethanesulfonate. MS (ESI) m/z 296.20 $[\text{M}+\text{H}]^+$.



Synthesis of 8-(2,2-difluoroethyl)-3-(5-ethynylpyridin-2-yl)-3,8-diazabicyclo[3.2.1]octane (S63).

To a suspension of Reactant 1 (0.2 g, 0.56 mmol) and 2-Iodo-1,1-difluoroethane (0.15 g, 0.78 mmol) in 1,4-Dioxane (3 ml) were added Cesium carbonate 99.95% (0.21 g, 3.35 mmol). The mixture was stirred at 60°C overnight. Cooled to room temperature and 2,2-Difluoroethyl trifluoromethane sulfonate(98%min) (0.17 g, 0.78 mmol) was added. The mixture was warmed up to 60°C for 8 h. Quenched with brine, extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered, concentrated and purified by silica column chromatography (10% EtOAc / Hex). The product was dissolved in Methanol (3 ml), potassium carbonate (0.11 g, 0.82 mmol) was added and after 1 h the mixture was concentrated diluted with EtOAc, washed with water, dried over Na₂SO₄, filtered concentrated to yield **S63** (76 mg, 99.7%). MS (ESI) m/z 278.2 $[\text{M}+\text{H}]^+$

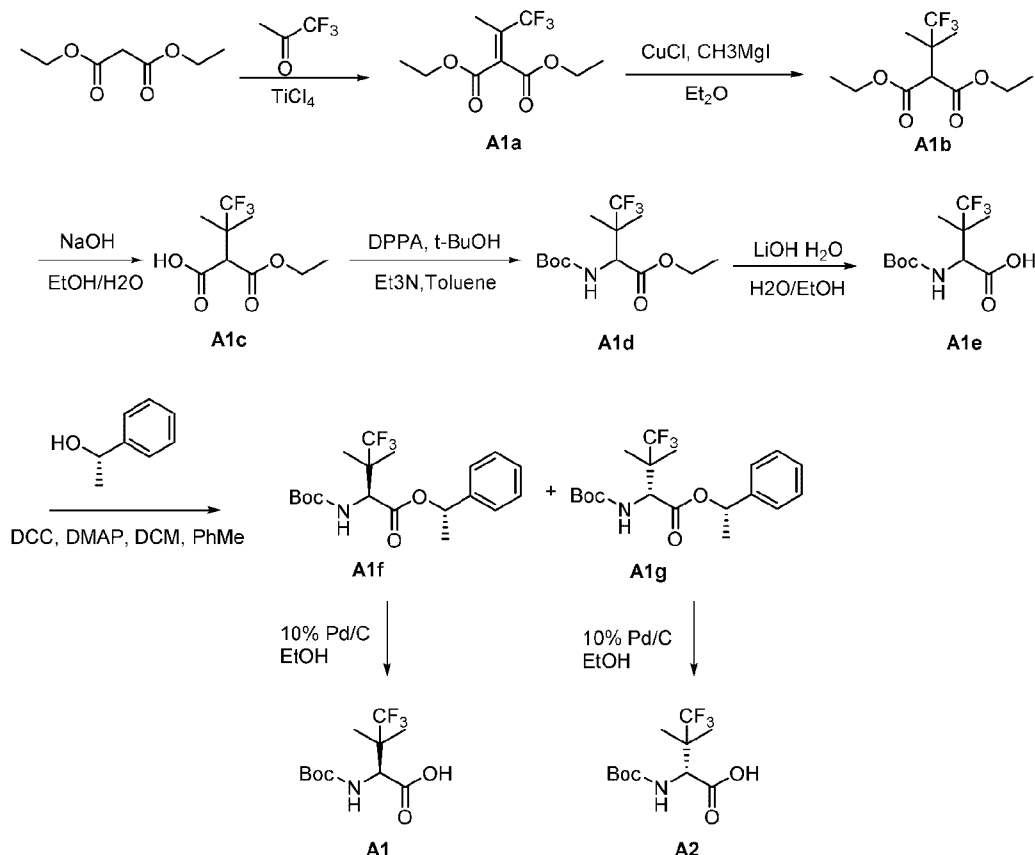


Synthesis 3-(5-ethynylpyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl(3-methyloxetan-3-yl)methanone (S64) To **S20a** suspended in CH₂Cl₂ (10 mL) was added 3-methyloxetan-3-carboxylic acid (0.12g, 1 mmol), Et₃N (0.68 ml, 5 mmol) followed by HATU (0.48 g, 1 mmol). The mixture was stirred for 1.5 h. The mixture was diluted with DCM and washed with water. The organic layer was dried over Na₂SO₄, and concentrated *in vacuo*. The residue was dissolved

in MeOH (20mL), cooled to 5 °C and potassium carbonate (0.4 g, 3 mmol) was added. After 30 min, the reaction quenched with water and brine, extracted into DCM, dried over Na₂SO₄, filtered, concentrated under reduced pressure and the residue was purified by silica column chromatography (60% - 100%EtOAc/hexanes to 5% MeOH / EtOAc) to give **S64**.

5 MS (ESI) m/z 312.22 [M+H].

2.3 SYNTHESIS OF A INTERMEDIATES



Synthesis of ethyl 2-(1,1,1-trifluoropropan-2-ylidene)malonate (A1a) A mixture of dry THF (5000 mL) and dry CCl₄ (600 mL) was cooled to 0 °C and treated with TiCl₄ (275 mL, 2.50 mol). The resulting yellow suspension was stirred at 0 °C for 5 min, treated sequentially with 1,1,1-trifluoropropan-2-one (140 g, 1.25 mol) and freshly distilled diethyl malonate (200 g, 1.25 mol), and then stirred at 0 °C for 0.5 hour. The reaction mixture was then treated with a solution of dry pyridine (400 mL) in dry THF (500 mL) and stirred at 0 °C for 1 hour and then at room temperature overnight. The reaction mixture was quenched with water and extracted with EtOAc (1 L x 3). The combined organic extracts were washed with brine and saturated NaHCO₃, dried

(MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc:PE = 1:50) to give the title compound **A1a** (298 g, 94%).
¹H NMR (CDCl₃, 300 MHz): δ 4.32-4.23 (m, 4H), 2.20 (s, 3H), 1.33-1.24 (m, 6H).

Synthesis of diethyl 2-(1,1,1-trifluoro-2-methylpropan-2-yl)malonate (A1b) A mixture of
 5 methylmagnesium iodide (3.0 mol/L in ether, 10 L, 30 mol) and cuprous chloride (3.5 g, 35 mmol) was stirred at 0 °C, treated with a solution of compound **A1a** (178 g, 700 mmol) in dry Et₂O (1000 mL) over 30 min, and stirred at rt for 30 min and then quenched with the dropwise addition of ice-water (1.5 L) followed by HCl aq (3 mol/L, 350 mL). The mixture was then
 10 extracted with Et₂O (1 L x 3). The combined organic extracts were washed with NaOH aq (1 N), water and brine, dried (MgSO₄), filtered and evaporated. The residue crude compound **A1b** (90 g, 47%) was used directly in next step without further purification. MS (ESI) m/z 271 [M+H]⁺.
¹H NMR (CDCl₃, 300 MHz): δ 4.22-4.15 (m, 4H), 3.64 (s, 1H), 1.38 (s, 6H), 1.30-1.24 (m, 6H).

Synthesis of 2-(ethoxycarbonyl)-4,4,4-trifluoro-3,3-dimethylbutanoic acid (A1c) A solution
 15 of compound **A1b** (144 g, 0.53 mol) in a mixture of EtOH (500 mL) and water (500 mL) was treated with NaOH (19 g, 0.48 mmol) in portions at 0 °C, and stirred at room temperature for 5 hours. The reaction mixture was evaporated to syrup, dissolved in water (1 L), and extracted with Et₂O (2 L). The aqueous phase was acidified with 1 M HCl to pH = 2.0 and extracted with EtOAc (1 L x 3). The combined organic extracts were washed with brine, dried (MgSO₄),
 20 filtered and evaporated to give the title compound **A1c** (107 g, 84%) which was used directly in next step without further purification. MS (ESI) m/z 241 [M+H]⁺.
¹H NMR (CDCl₃, 300 MHz): δ 4.23 (q, *J* = 5.4 Hz, 2H), 3.69 (s, 1H), 1.40 (s, 6H), 1.27 (t, *J* = 5.1 Hz, 3H).

Synthesis of ethyl 2-((*tert*-butoxycarbonyl)amino)-4,4,4-trifluoro-3,3-dimethylbutanoate (A1d) A solution of compound **A1c** (110 g, 454 mmol) in dry toluene (600 mL) was treated with
 25 triethylamine (45.4 g, 454 mmol) and diphenylphosphoryl azide (125 g, 454 mmol), the reaction mixture was refluxed for 1 hour, then *t*-BuOH (46.7 g, 630 mmol) was added in. The mixture was refluxed overnight. Cooled to rt, the solvent was evaporated and the residue was dissolved in EtOAc (1 L), washed with 5% NaHCO₃ solution, dried (MgSO₄), filtered and evaporated. The remainder was purified by column chromatography on silica gel (EtOAc:PE = 1:9) to give crude
 30 compound **A1d** (60 g, 46%), which was used directly in next step without further purification. MS (ESI) m/z 313 [M+H]⁺.
¹H NMR (CDCl₃, 300 MHz): δ 5.20 (d, *J* = 5.7 Hz, 1H), 4.44 (d, *J* = 10.8 Hz, 1H), 4.25-4.16 (m, 2H), 1.44 (s, 9H), 1.39-1.26 (m, 6H), 1.19 (m, 3H).

Synthesis of 2-((*tert*-butoxycarbonyl)amino)-4,4,4-trifluoro-3,3-dimethylbutanoic acid (A1e) To a solution of compound **A1d** (380 g, 1214 mmol) in water (2000 mL) and ethanol

(2000 mL) was added LiOH.H₂O (134 g, 3166 mmol). The mixture was stirred overnight. Diluted with EtOAc, acidify to pH = 2, extracted with EtOAc (2000 mL x 3). The organic layer was washed with brine, dried over MgSO₄, and concentrated to afford compound **A1e** (300 g, 86%) as a white solid. ¹H NMR (CDCl₃, 300 MHz): δ 5.20 (d, *J* = 10.2 Hz, 1H), 4.48 (d, *J* = 10.2 Hz, 1H), 1.45 (s, 9H), 1.30 (s, 3H), 1.25 (s, 3H).

Synthesis of (S)-(S)-1-phenylethyl 2-((tert-butoxycarbonyl)amino)-4,4,4-trifluoro-3,3-dimethylbutanoate (A1g) The acid **A1e** (300 g, 1052 mmol) and (*N,N'*-

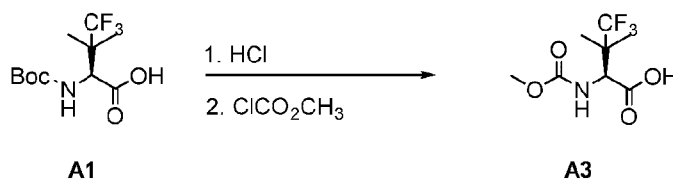
Dicyclohexylcarbodiimide (325 g, 1578 mmol) were combined in DCM (250 mL) and PhMe (4000 mL). The solution was cooled to 0 °C, and then 4-(Dimethylamino)pyridine (128 g, 1052 mmol) and (*S*)-(-)-1-Phenylethanol (128 g, 1052 mmol) were added and the mixture was allowed to warm to room temperature and stirred overnight. The mixture was concentrated, and then the residue was taken up in EtOAc/water, and extracted with EtOAc (2000 mL x 3). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. The crude was purified by column chromatography on silica gel (0-8% EtOAc/PE) to get two compounds. The mixture of diastereomers was separated by chiral column (IA; Heptane;IPA (70:30)). First peak was collected to get the compound **A1f** (105 g, 25%) and the second peak was collected to get the compound **A1g** (80 g, 19%). ¹H NMR of compound **A1f** (CDCl₃, 300 MHz): δ 7.38-7.31 (m, 5H), 5.90 (q, *J* = 6.3 Hz, 1H), 5.18 (d, *J* = 9.6 Hz, 1H), 4.48 (d, *J* = 9.6 Hz, 1H), 1.56 (d, *J* = 6.9 Hz, 3H), 1.44 (s, 9H), 1.31 (s, 3H), 1.21 (s, 3H). ¹H NMR of compound **A1g** (CDCl₃, 300 MHz): δ 7.34-7.30 (m, 5H), 5.92 (q, *J* = 6.3 Hz, 1H), 5.20 (d, *J* = 9.6 Hz, 1H), 4.44 (d, *J* = 9.6 Hz, 1H), 1.58 (d, *J* = 6.9 Hz, 3H), 1.45 (s, 9H), 1.21 (s, 3H), 1.11 (s, 3H).

Synthesis of (S)-2-((tert-butoxycarbonyl)amino)-4,4,4-trifluoro-3,3-dimethylbutanoic acid (A1) The compound **A1f** (83 g, 214 mmol) was diluted with ethanol (1000 mL). Pd/C (10%,

wet, 17 g) was added and the atmosphere was replaced with hydrogen. After stirring for 5 hours, the mixture was filtered over celite, washing with EtOAc and the filtrate was concentrated to get product **A1** (50 g, 82%). MS (ESI) *m/z* 186 [M-Boc +1]⁺. ¹H NMR (300 MHz, DMSO-*d*₆): δ 12.98 (br s, 1H), 7.18 (d, *J* = 9.6 Hz, 1H), 4.27 (d, *J* = 9.9 Hz, 1H), 1.36 (s, 9H), 1.14 (s, 6H).

Synthesis of (R)-2-((tert-butoxycarbonyl)amino)-4,4,4-trifluoro-3,3-dimethylbutanoic acid (A2) The compound **A1g** (80 g, 205 mmol) was diluted with ethanol (800 mL). Pd/C (10%, wet,

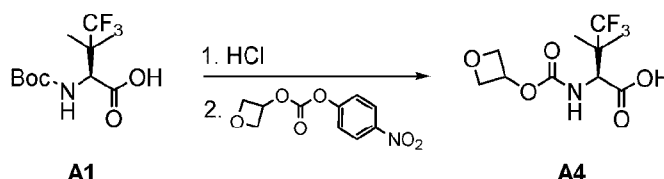
15 g) was added and the atmosphere was replaced with hydrogen. After stirring for 5 hours, the mixture was filtered over celite, washing with EtOAc and the filtrate was concentrated to get product **A2** (45 g, 77%). MS (ESI) *m/z* 186 [M-Boc +1]⁺. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.18 (d, *J* = 9.6 Hz, 1H), 4.25 (d, *J* = 9.9 Hz, 1H), 1.36 (s, 9H), 1.14 (s, 6H).



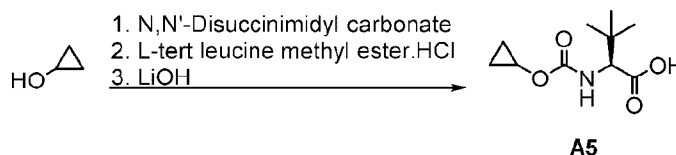
Synthesis of (S)-4, 4, 4-trifluoro-2-((methoxycarbonyl) amino)-3, 3-dimethylbutanoic acid

(A3) To a solution of **A1** (10 g, 35.06 mmol) in DCM (160 mL) and MeOH (40 mL), was added HCl (4.0M in dioxane, 40 mL). The reaction was stirred at room temperature overnight. The

- 5 reaction was concentrated to dryness (foamy). The residue was dissolved in a mixture of dioxane and 2M NaOH (90 mL), stirred for 5 min, and then add methyl chloroformate (5.7 mL, 73.33 mmol). After 4 h the reaction was extracted with 2 x 100 mL DCM (discard organics) and the aqueous layer was adjusted to pH ~2 with 4M HCl (~50 mL). The aqueous layer was extracted with 2 x 150 mL EtOAc, the combined EtOAc layers were dried over sodium sulfate, filtered, and concentrated to give **A3** (8.54 g, 100%). MS (ESI) m/z 244.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 4.57 - 4.41 (m, 1H), 3.66 (d, J = 2.1 Hz, 5H), 1.25 (d, J = 10.0 Hz, 7H).



- 15 **Synthesis of (S)-4,4,4-trifluoro-3,3-dimethyl-2-(((oxetan-3-yloxy)carbonyl)amino)butanoic acid (A4).** The title compound **A4** was prepared according to the method presented for the synthesis of compound **A3** but instead utilizing 4-nitrophenyl oxetan-3-yl carbonate. MS (ESI) m/z 285.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 7.66 (d, J = 9.9 Hz, 1H), 5.37 (tt, J = 6.3, 5.1 Hz, 1H), 4.87 - 4.82 (m, 2H), 4.62 (tdd, J = 7.5, 5.1, 0.9 Hz, 2H), 4.49 - 4.41 (m, 1H), 1.28 (s, 3H), 1.25 (s, 3H).

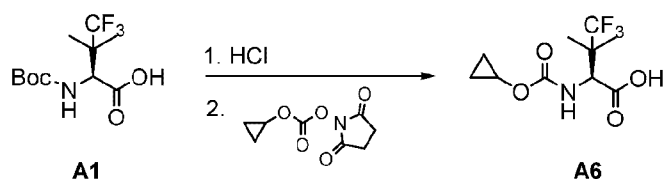


Synthesis of (S)-2-((cyclopropoxycarbonyl) amino)-3, 3-dimethylbutanoic acid (A5)

To a solution of cyclopropanol (0.4 ml, 6.37 mmol) in CH_3CN (18 mL) at 0°C, was added bis(2,5-

- 25 dioxopyrrolidin-1-yl) carbonate (DSC) (3.26 g, 12.74 mmol) followed by Et_3N (2.66 ml, 19.11

mmol). The reaction mixture was warmed up to 40°C and stirred overnight. After cooling to room temperature, the reaction was concentrated under reduced pressure and the residue triturated with DCM, the solid filtered, and the filtrate was purified by silica column chromatography (10% - 100% EtOAc/hexanes). The product (663 mg, 3.33 mmol) was dissolved in THF (5 mL) and L-tert-leucine methyl ester hydrochloride (0.91 g, 5 mmol) and Et₃N (1.39 ml, 0.01 mol) were added, the reaction was warmed up to 40°C for 18 h, then at room temperature for 48 h, diluted with EtOAc, washed with water. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure and the residue (760 mg, 3.31 mmol) was dissolved in a mixture of Methanol (4 mL) / water (2 mL), lithium hydroxide, monohydrate (0.56 g, 0.01 mol) was added. After 16 h, the mixture was concentrated, diluted with EtOAc, washed with brine, the organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford **A5**. ¹H NMR (400 MHz, Chloroform-*d*) δ 4.19 (d, *J* = 9.6 Hz, 1H), 1.02 (s, 11H), 0.68 (d, *J* = 4.8 Hz, 5H).

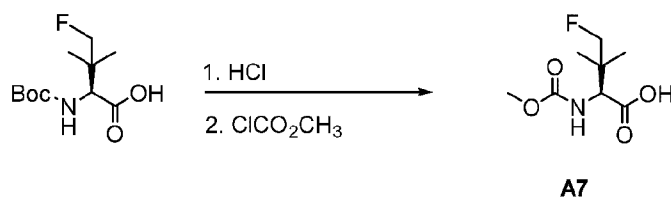


15

Synthesis of (S)-2-((cyclopropoxycarbonyl)amino)-4,4,4-trifluoro-3,3-dimethylbutanoic acid (**A6**)

The title compound **A6** was prepared according to the method presented for the synthesis of compound **A3** but instead utilizing cyclopropyl (2,5-dioxopyrrolidin-1-yl) carbonate. ¹H NMR (400 MHz, Chloroform-*d*) δ 5.33 (d, *J* = 9.8 Hz, 1H), 4.53 (d, *J* = 9.9 Hz, 1H), 4.08 – 4.01 (m, 1H), 1.35 (s, 3H), 1.26 (s, 3H), 0.81 – 0.52 (m, 4H).

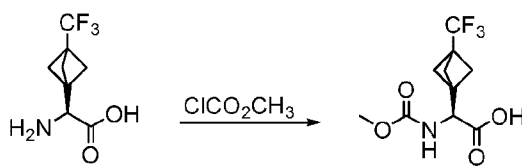
20



Synthesis of (S)-4-fluoro-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoic acid (**A7**)

The title compound **A7** was prepared according to the method presented for the synthesis of compound **A3** but instead utilizing (S)-2-((tert-butoxycarbonyl)amino)-4-fluoro-3,3-dimethylbutanoic acid (US 2013/0183629 A1 (pp. 178-179))

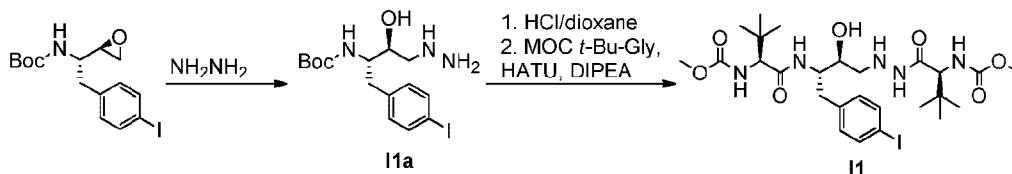
25

**A8**

Synthesis of (S)-2-((methoxycarbonyl)amino)-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetic acid (A8). The title compound **A8** was prepared according to the method presented for the synthesis of compound **A3** but instead utilizing (S)-2-amino-2-(3-

- 5 (trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetic acid. MS (ESI) m/z 267.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 4.35 - 4.26 (m, 1H), 3.65 (s, 3H), 1.97 (qd, $J = 9.6, 1.7$ Hz, 6H).

2.4 SYNTHESIS OF I INTERMEDIATES



10

Synthesis of *tert*-butyl ((2*S*,3*S*)-4-hydrazinyl-3-hydroxy-1-(4-iodophenyl)butan-2-yl)

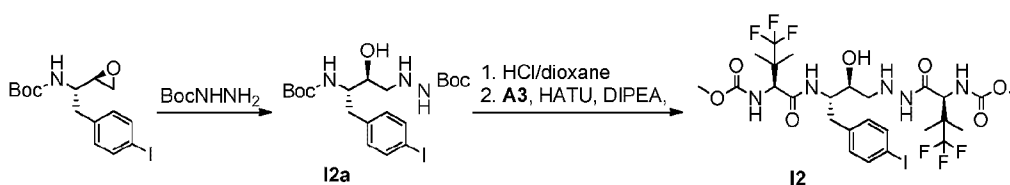
carbamate (I1a). To a solution of the NH_2NH_2 (48.3 g, 0.82 mol) in $iPrOH$ (157 mL) was added *tert*-butyl ((S)-2-(4-iodophenyl)-1-((R)-oxiran-2-yl)ethyl)carbamate (16.1 g, 41.4 mmol) dissolved in DCM (79 mL) dropwise over 1 h at 0 °C. The ice bath was removed and the

15 reaction mixture was stirred at rt for 16 h. The mixture was evaporated solvents, diluted with water, filtrated, washed with water and dried to give compound **I1a** (17.0 g, 97%). 1H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, $J = 7.8$ Hz, 2H), 7.02-6.96 (m, 2H), 5.03 (d, $J = 9.9$ Hz, 1H), 3.78-3.66 (m, 2H), 2.85-2.67 (m, 4H), 2.04 (s, 3H), 1.38 (s, 9H).

Synthesis of ((S)-1-((1*S*,2*S*)-2-hydroxy-1-(4-iodo-benzyl)-3-[*N'*-((S)-2-methoxy

- 20 **carbonylamino-3,3-dimethyl-butyryl)-hydrazino]-propylcarbamoyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester (I1).** To a solution of the **I1a** (34.0 g, 80.7 mmol) in CH_2Cl_2 (990 mL) at room temperature was added 4 M hydrochloric acid (198 mL). After stirring for 2 h at 45 °C, LC/MS indicated completion of the reaction and the mixture was concentrated *in vacuo*. To this crude residue suspended in CH_2Cl_2 (700 mL) and cooled to -20°C was added DIPEA (48.2 g, 373.9 mmol), Moc-*t*Bu-Gly (25.53 g, 135.1 mmol) followed by HATU (53.4 g, 140.5 mmol).
- 25 The mixture was warmed up to room temperature slowly and stirred for 1 h. The mixture was

diluted with DCM (1 L) and washed with aqueous 1N HCl solution (400 mL), aqueous saturated NaHCO₃ solution (400 mL), water (600 mL x 2), and brine (600 mL) in sequence. The organic layer was dried over Na₂SO₄, and concentrated *in vacuo* to give the residue which was purified by column chromatography on silica gel eluted with EtOAc: petroleum ether = 2:1 to 100% of EtOAc to EtOAc: MeOH = 50: 1 to give product **11** (8.2 g, 19.4%). MS (ESI) *m/z* 664.0 [M+H]⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 4.10-4.21 (m, 1H), 3.90 (s, 1H), 3.82 (s, 1H), 3.69-3.64 (m, 7H), 2.78-2.76 (m, 4H), 0.95 (s, 9H), 0.91 (s, 9H);

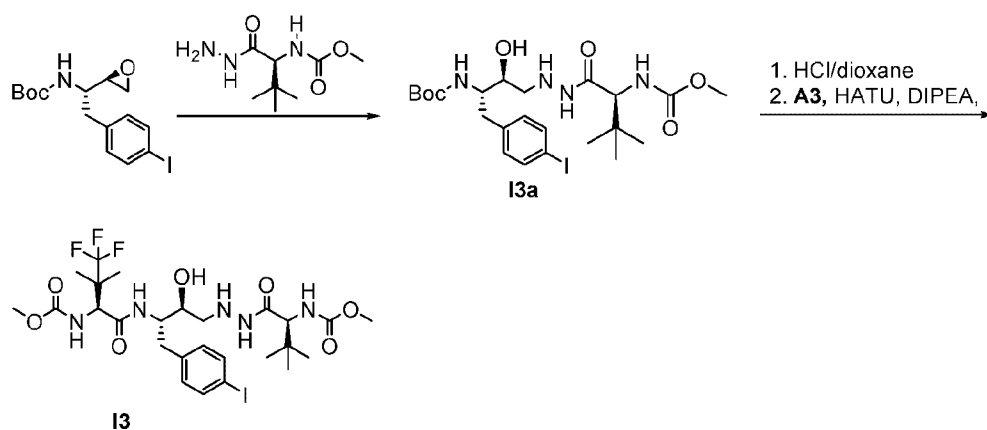


Synthesis of tert-butyl 2-((2S,3S)-3-((tert-butoxycarbonyl)amino)-2-hydroxy-4-iodophenyl)butyl hydrazine-1-carboxylate (12a**)**

A mixture of tert-butyl ((S)-2-(4-iodophenyl)-1-((R)-oxiran-2-yl)ethyl)carbamate (5 g, 12.85 mmol) and tert-butylhydrazinecarboxylate (3.4 g, 25.69 mmol) in isopropanol (60 mL) was heated to 80°C for 48h, then cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica column chromatography (0% to 40% EtOAc/DCM) to afford **12a** (4.86 g, 72.6%) MS (ESI) *m/z* 522.19 [M+H]⁺

Synthesis of methyl ((5S,10S,11S,14S)-16,16,16-trifluoro-10-hydroxy-11-(4-iodobenzyl)-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,8,12-

tetraazahexadecan-14-yl)carbamate (12**)** **12a** (5.0 g, 10 mmol) was dissolved in DCM (15 mL) and HCl (4.0M in dioxane, 36 mL). The reaction was stirred overnight then concentrated under reduce pressure. To the residue was added **A3** (4.96 g, 20 mmol) and HATU (8.02 g, 21 mmol) in DCM (100 mL), followed by N, N-diisopropylethylamine (16.7 ml, 96 mmol). The reaction was stirred at stirred at room temperature overnight. The reaction mixture was diluted with DCM and washed with saturated NaHCO₃, and brine then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (2% to 5% MeOH/DCM) to afford **12** (7.39g, 60%) MS (ESI) *m/z* 773.0 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 7.52 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.2 Hz, 2H), 3.71 (q, *J* = 6.9 Hz, 7H), 3.65 (s, 3H), 1.37 (dd, *J* = 7.0, 1.7 Hz, 32H), 1.19 - 1.07 (m, 10H).

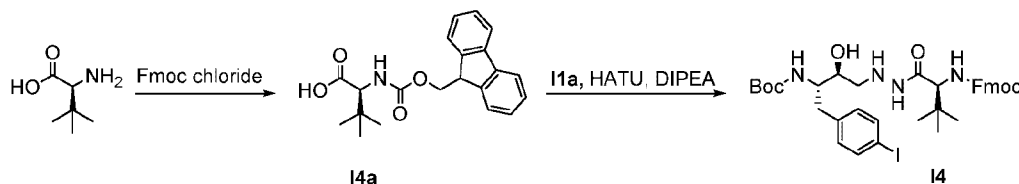


Synthesis of tert-butyl ((2S,3S)-3-hydroxy-1-(4-iodophenyl)-4-(2-((S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)hydrazinyl)butan-2-yl)carbamate (13a).

The title compound **13a** was prepared according to the method presented for the synthesis of compound **11** but instead utilizing methyl (S)-(1-hydrazinyl-3,3-dimethyl-1-oxobutan-2-yl)carbamate. MS (ESI) m/z 593.1 $[M+H]^+$.

Synthesis of methyl ((5S,10S,11S,14S)-5-(tert-butyl)-16,16,16-trifluoro-10-hydroxy-11-(4-iodobenzyl)-15,15-dimethyl-3,6,13-trioxo-2-oxa-4,7,8,12-tetraazahexadecan-14-yl)carbamate

The title compound **13** was prepared according to the method presented for the synthesis of compound **12** but instead utilizing **13a** and **A3**. MS (ESI) m/z 718.7 $[M+H]^+$.



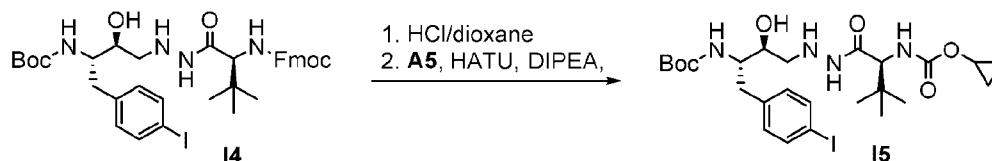
Synthesis of (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3,3-dimethylbutanoic acid (14a)

L-tert-Leucine (2 g, 15.25 mmol) was dissolved in 10% Na_2CO_3 solution (80 ml), the solution was cooled to 0°C , then added 9-Fluorenylmethyl chloroformate (4.77 g, 18.44 mmol) in dioxane (31 mL). After 2 h, the reaction mixture was diluted with water, washed with ether and the aqueous layer was adjusted to pH ~ 2 with 6N HCl and extracted with EtOAc. The combined EtOAc layers were dried over Na_2SO_4 , filtered, and concentrated to give **14a**. MS (ESI) m/z 353.8 $[M+H]^+$.

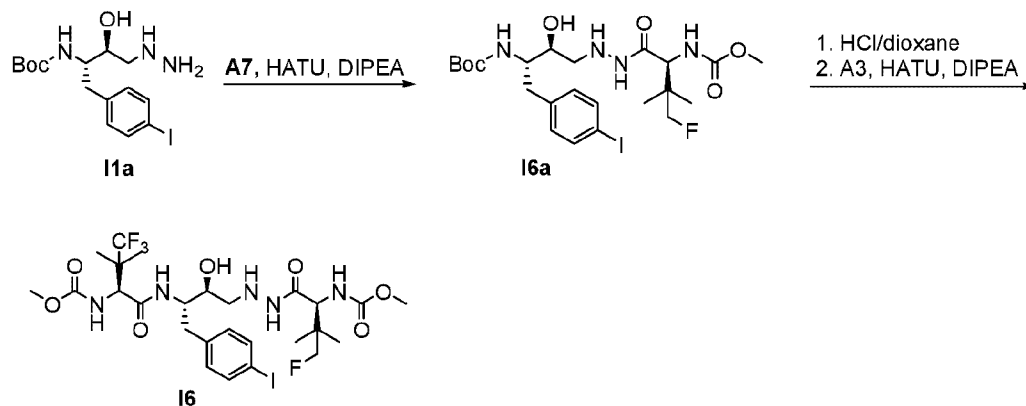
Synthesis of (9H-fluoren-9-yl)methyl ((S)-1-(2-((2S,3S)-3-((tert-butoxycarbonyl)amino)-2-hydroxy-4-(4-iodophenyl)butyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (14)

To **14a** (2.55 g, 7.22 mmol) was added **11a** (3 g, 7.12 mmol), HATU (2.7 g, 7.1 mmol) and a

mixture of $\text{CH}_2\text{Cl}_2/\text{DMF}$ (2:1) (75 ml) followed by N,N -diisopropylethylamine (3 ml, 17.22 mmol). The reaction was stirred at room temperature for 4 h. The reaction mixture was diluted with EtOAc and washed with saturated NH_4Cl , and brine then dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (2% to 5% MeOH/DCM) to afford **14** (2.38 g, 44%) MS (ESI) m/z 757.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.01 (s, 1H), 7.75 (t, $J = 7.5$ Hz, 5H), 7.66 - 7.46 (m, 6H), 7.38 (q, $J = 7.5$ Hz, 4H), 7.34 - 7.27 (m, 1H), 6.95 (dd, $J = 16.8, 8.0$ Hz, 4H), 5.52 (d, $J = 47.2$ Hz, 2H), 5.01 (dd, $J = 19.2, 10.0$ Hz, 1H), 4.48 (dd, $J = 10.5, 6.5$ Hz, 1H), 4.34 (dt, $J = 28.9, 9.8$ Hz, 2H), 4.19 (t, $J = 6.8$ Hz, 2H), 3.91 (dd, $J = 45.4, 14.8$ Hz, 2H), 3.60 (d, $J = 31.0$ Hz, 2H), 1.39 (d, $J = 16.0$ Hz, 13H).



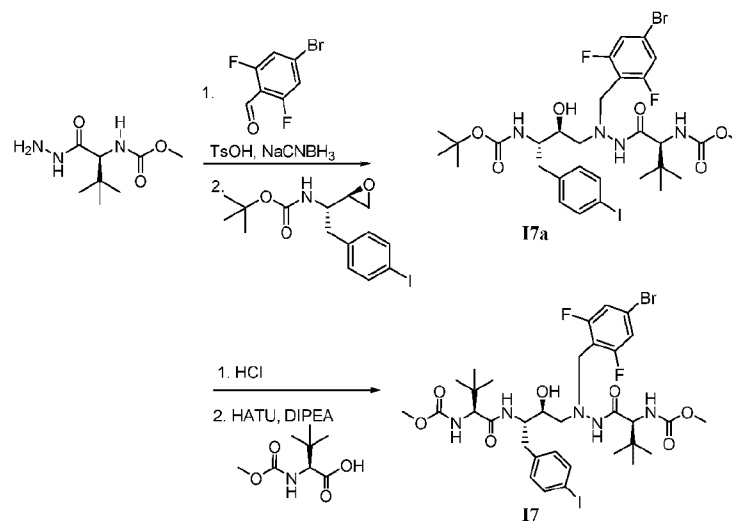
Synthesis of tert-butyl ((2S,3S)-4-(2-((S)-2-((cyclopropoxycarbonyl)amino)-3,3-dimethylbutanoyl)hydrazinyl)-3-hydroxy-1-(4-iodophenyl)butan-2-yl)carbamate (15**)** The title compound **15** was prepared according to the method presented for the synthesis of compound **12** but instead utilizing **14** and **A5**. MS (ESI) m/z 619.4 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.02 (s, 0H), 7.59 (d, $J = 8.0$ Hz, 2H), 7.00 (d, $J = 7.9$ Hz, 2H), 5.37 (s, 1H), 5.04 (s, 1H), 4.02 (s, 1H), 3.83 (s, 1H), 3.74 - 3.58 (m, 1H), 2.95 (s, 1H), 2.88 (d, $J = 0.7$ Hz, 1H), 2.85 (d, $J = 7.7$ Hz, 1H), 2.80 (s, 6H), 1.38 (s, 8H), 1.01 (d, $J = 10.5$ Hz, 1H), 0.90 (s, 8H), 0.66 (d, $J = 4.7$ Hz, 4H).



Synthesis of tert-butyl ((2S,3S)-4-(2-((S)-4-fluoro-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)hydrazinyl)-3-hydroxy-1-(4-iodophenyl)butan-2-yl)carbamate (I6a). The title compound **I6a** was prepared according to the method presented for the synthesis of

compound **I4** but instead utilizing **A7**. MS (ESI) m/z 611.5 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 7.57 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.1 Hz, 2H), 5.50 (s, 1H), 4.97 (d, J = 9.8 Hz, 1H), 4.37 - 4.17 (m, 1H), 4.03 (td, J = 25.3, 23.8, 9.4 Hz, 2H), 3.68 (s, 4H), 3.50 (s, 0H), 3.17 (qd, J = 7.4, 4.4 Hz, 1H), 2.94 (s, 1H), 2.82 (dt, J = 15.8, 5.5 Hz, 4H), 1.50 (t, J = 7.4 Hz, 1H), 1.46 (dd, J = 17.4, 6.7 Hz, 3H), 1.39 (s, 9H), 0.96 (s, 5H).

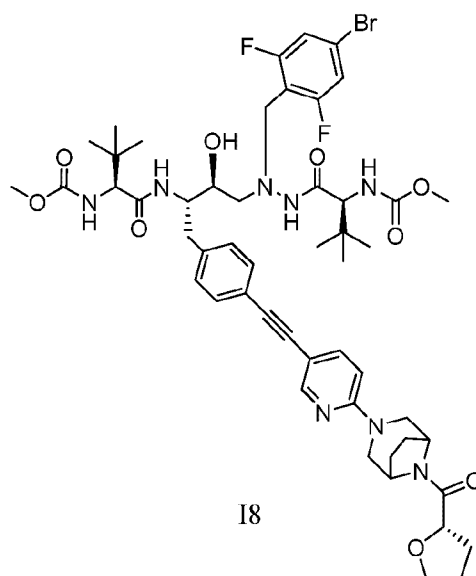
Synthesis of methyl ((5S,8S,9S,14S)-16-fluoro-9-hydroxy-8-(4-iodobenzyl)-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (I6). The title compound **I6** was prepared according to the method presented for the synthesis of compound **I2** but instead utilizing **I6a**. MS (ESI) m/z 736.1 $[M+H]^+$.



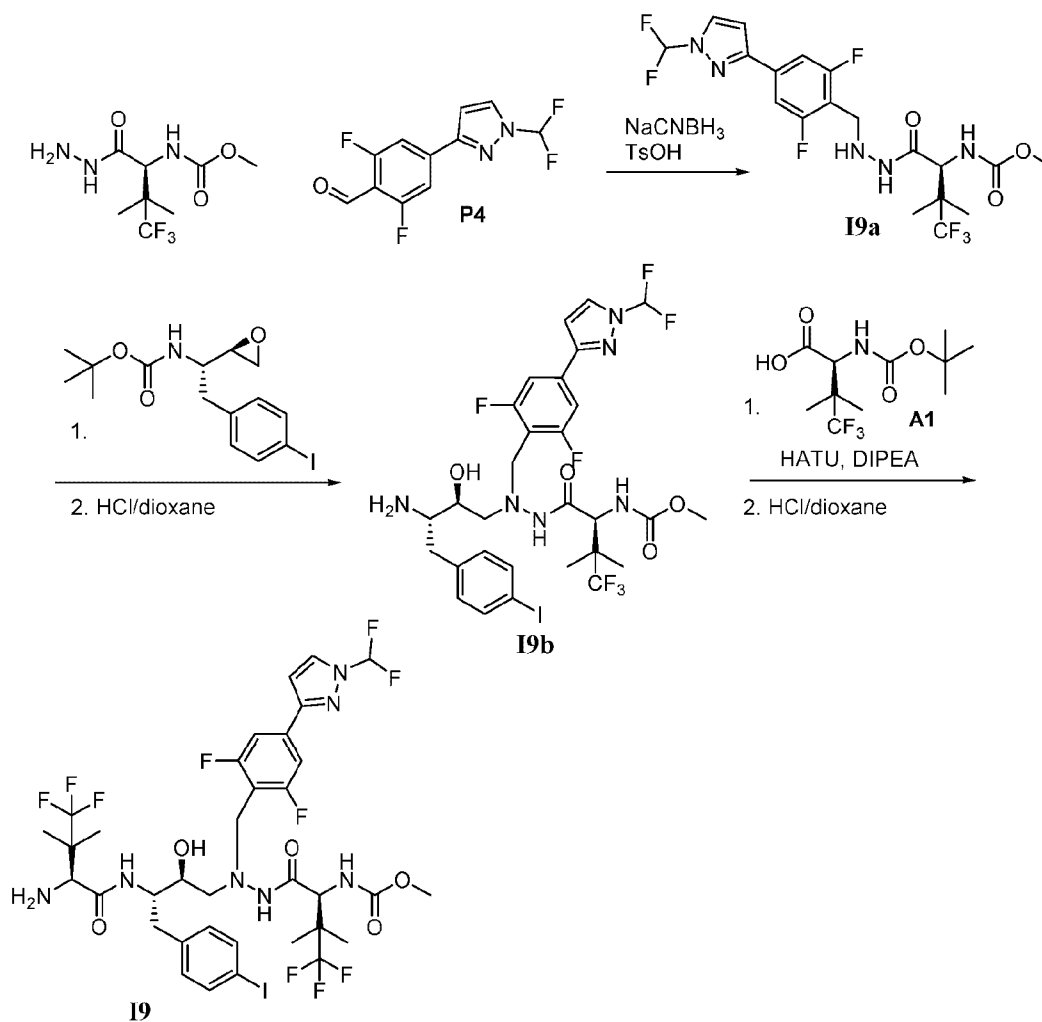
Synthesis of methyl ((5S,8S,9S,14S)-11-(4-bromo-2,6-difluorobenzyl)-5-(tert-butyl)-9-hydroxy-8-(4-iodobenzyl)-15,15-dimethyl-3,6,13-trioxo-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (I7). Methyl (S)-((1-hydrazinyl-3,3-dimethyl-1-oxobutan-2-yl)carbamate (9.2g, 45 mmol) and 4-bromo-2,6-difluorobenzaldehyde (10 g, 45 mmol) were stirred in THF at room temperature for 60 minutes. 4-methylbenzenesulfonic acid monohydrate (9.0 g, 48 mmol) was added and the mixture was stirred for an additional 75 minutes. The mixture was cooled to 8 °C, followed by addition of NaCNBH₃ (3.8 g, 61 mmol). The reaction was observed to exotherm to 30 °C. The mixture was stirred for 4 hours at room followed by dilution with DCM (200 mL) and quenching with 1M K₃PO₄ to pH 12. The organic layer was separated, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was combined with tert-butyl ((S)-2-(4-

iodophenyl)-1-((R)-oxiran-2-yl)ethyl)carbamate (8.5 g, 22 mmol) in isopropanol (30 mL) and heptanes (40 mL). The mixture was stirred at reflux for 40 hours, after which time it was cooled to room temperature and diluted with 15 mL hexanes. The product (**I7a**) was collected by filtration and the solids rinsed with 20% IPA in hexanes. MS (ESI) m/z 797.8 $[M+H]^+$.

- 5 The title compound **I7** was prepared according to the method presented for the synthesis of compound **I1** but instead utilizing methyl (S)-(1-(2-(4-bromo-2,6-difluorobenzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**I7a**) MS (ESI) m/z 869.72 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 7.53 (d, $J = 7.9$ Hz, 2H), 7.16 (d, $J = 6.9$ Hz, 2H), 7.00 (d, $J = 8.2$ Hz, 2H), 4.16 – 4.03 (m, 2H), 3.95 – 3.83 (m, 2H), 3.76 – 3.57 (m, 11H), 2.90 – 2.72 (m, 6H), 0.86 (d, $J =$
10 23.1 Hz, 18H).



- Synthesis of methyl ((5S,8S,9S,14S)-11-(4-bromo-2,6-difluorobenzyl)-5-(tert-butyl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-(4-((6-((S)-tetrahydrofuran-2-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (**I8**). Intermediates: **I7**, and **S25**. MS (ESI) m/z 1052.92 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.19 (s, 1H), 7.79 (d, $J = 8.8$ Hz, 2H), 7.35 (d, $J = 7.8$ Hz, 2H), 7.23 (d, $J = 8.1$ Hz, 2H), 7.17 (d, $J = 6.9$ Hz, 2H), 6.98 (t, $J = 10.5$ Hz, 1H), 4.69 (t, $J = 6.8$ Hz, 2H), 4.21 – 4.00 (m, 4H), 3.98 – 3.81 (m, 5H), 3.80 – 3.62 (m, 9H), 3.25 – 3.09 (m, 2H), 2.98 – 2.85 (m, 2H), 2.79 (d, $J = 6.6$ Hz, 2H), 2.30 – 2.08 (m, 1H), 2.02 – 1.72 (m, 6H),
15 0.87 (d, $J = 21.7$ Hz, 22H).



Methyl ((S)-1-(2-((2S,3S)-3-((S)-2-amino-4,4,4-trifluoro-3,3-dimethylbutanamido)-2-hydroxy-4-(4-iodophenyl)butyl)-2-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)hydrazinyl)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)carbamate (19). A

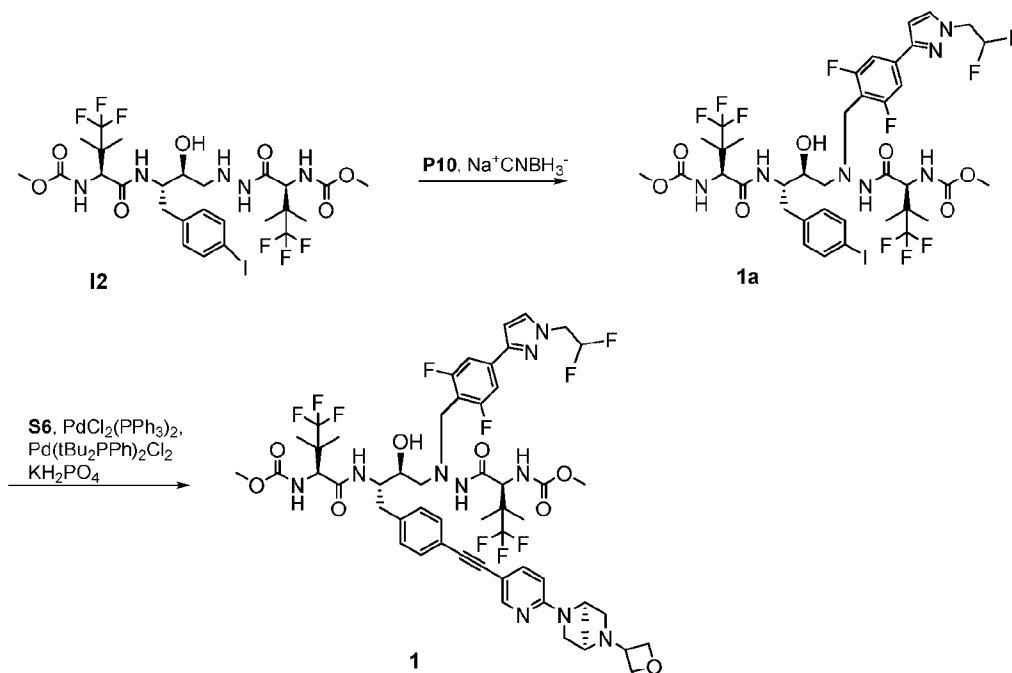
- 5 solution of methyl (S)-((S)-1-((2S,3S)-3-((S)-2-amino-4,4,4-trifluoro-3,3-dimethylbutanamido)-2-hydroxy-4-(4-iodophenyl)butyl)-2-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)hydrazinyl)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)carbamate HCl salt (200 mg, 0.68 mmol) and 4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzaldehyde (P4) (190 mg, 0.75 mmol) in ethanol (5 mL) and acetic acid (0.5 mL) was stirred at 50 °C for 1 hour. The reaction was then cooled to room temperature, diluted with EtOAc, rinsed with aq NaHCO₃, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The
- 10 crude mixture was redissolved in MeTHF (10 mL) and cooled to 5 °C. SODIUM CYANOBOROHYDRIDE (64 mg, 1.0 mmol) was added followed by 4-methylbenzenesulfonic acid monohydrate (155 mg, 0.82 mmol). After 1 hour, the reaction was warmed to room temperature and additional SODIUM CYANOBOROHYDRIDE (64 mg, 1.0 mmol) and 4-methylbenzenesulfonic acid monohydrate (155 mg, 0.82 mmol) were added. After an additional

30 minutes, the reaction was quenched with 2M NaOH to pH 14. The mixture was then stirred at 40 °C for 30 minutes. The mixture was cooled to room temperature, diluted with EtOAc, and the aqueous layer was removed. The organic layer was dried over Na₂SO₄, filtered, concentrated *in vacuo*, and purified by column chromatography (30% → 70% EtOAc in hexanes) to provide

- 5 methyl (S)-(1-(2-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)hydrazinyl)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)carbamate (I9a). ¹H NMR (400 MHz, Chloroform-d) δ 7.87 (d, J = 2.8 Hz, 1H), 7.35 (d, J = 7.9 Hz, 2H), 7.22 (t, J = 60.7 Hz, 1H), 6.72 (d, J = 2.8 Hz, 1H), 5.34 (d, J = 9.7 Hz, 1H), 4.30 (d, J = 9.7 Hz, 1H), 4.17 (d, J = 12.9 Hz, 1H), 4.06 (d, J = 13.0 Hz, 1H), 3.67 (s, 3H), 1.23 (s, 3H), 1.16 (s, 3H). MS (ESI) m/z 499.2 [M+H].
- 10 Methyl (S)-(1-(2-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)hydrazinyl)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)carbamate (I9a) (0.25 g, 0.50 mmol) was combined with tert-butyl ((S)-2-(4-iodophenyl)-1-((R)-oxiran-2-yl)ethyl)carbamate (0.21 g, 0.55 mmol) in heptanes (4 mL) and IPA (2 mL). The mixture was stirred at 90 °C in a sealed tube overnight. The crude mixture was cooled to room temperature, concentrated *in vacuo*, and redissolved in
- 15 DCM (10 mL), and cooled to 5 °C. 4M Hydrochloric acid (4.0M in dioxane, 0.89 ml) was added and the mixture was stirred overnight, allowing to slowly warm to room temperature. Concentration *in vacuo* provided methyl ((S)-1-(2-((2S,3S)-3-amino-2-hydroxy-4-(4-iodophenyl)butyl)-2-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)hydrazinyl)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**I9b**) as an HCl salt. MS (ESI) m/z
- 20 787.9 [M+H]. This crude salt (I9b) was combined in DCM (5 mL) with (S)-2-((tert-butoxycarbonyl)amino)-4,4,4-trifluoro-3,3-dimethylbutanoic acid (A1) (0.11 g, 0.38 mmol) and DIPEA (0.27 ml, 2 mmol). HATU (0.14 g, 0.36 mmol) was added. After 20 minutes the reaction was quenched with aq NaOH, the organic layer was separated, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The resulting mixture was redissolved in DCM and 4M HCl in dioxane
- 25 (0.76 ml) was added. After 3.5 hours, the mixture was concentrated *in vacuo* to provide methyl ((S)-1-(2-((2S,3S)-3-((S)-2-amino-4,4,4-trifluoro-3,3-dimethylbutanamido)-2-hydroxy-4-(4-iodophenyl)butyl)-2-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)hydrazinyl)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)carbamate as an HCl salt that was used without further purification. MS (ESI) m/z 956.2 [M+H].

30

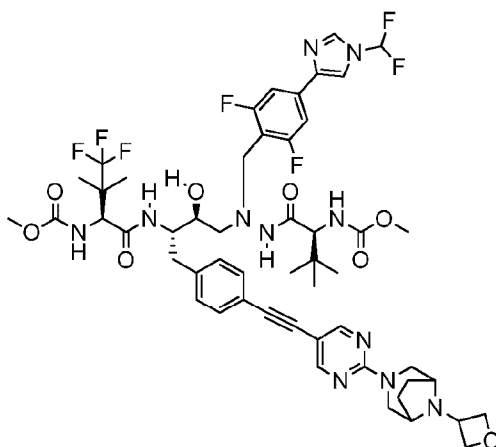
3. Example Compounds, Synthesis, and Characterization

EXAMPLE 1

Synthesis of methyl ((5S,10S,11S,14S)-8-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-10-hydroxy-11-(4-iodobenzyl)-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,8,12-tetraazahexadecan-14-yl)carbamate (1a). Combined **P10** (289.23 mg, 0.88 mmol) and **I2** (486 mg, 0.63 mmol) were stirred in a 3:1 mixture of THF/AcOH (7.0 mL) at 55°C for 1h. The mixture was cooled to room temperature and polymer supported sodium cyanoborohydride (2.49mmol/g, 780.02 mg, 1.94 mmol) was added and the reaction mixture was stirred at room temperature for 2h, and then at 10 28 °C overnight and 35 °C for 3h. The mixture was cooled to room temperature, filtered, concentrated under reduced pressure and the residue was purified by column chromatography (45% to 75% EtOAc/Hexanes) to afford **1a** MS (ESI) m/z 1028.3 [M+H]⁺.

Synthesis of methyl ((5S,10S,11S,14S)-8-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-10-hydroxy-15,15-dimethyl-11-(4-((6-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,8,12-tetraazahexadecan-14-yl)carbamate (1) In a vial, a solution of **1a** (28 mg, 0.027 mmol), **S6** (10.4 mg, 0.041 mmol), copper (I) iodide (0.52 mg, 0.002 mmol), trans-Dichlorobis(triphenylphosphine)palladium (II) (99%, 0.87 mg, 0.004 mmol) in a mixture of and MeCN : Et₃N 3:1(1mL) was degassed and then heated to 25 °C for 25 min. 20 Concentrated under reduced pressure. The residue was purified by HPLC and Lyophilized to

give **1**. MS (ESI) m/z 1131.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.19 (s, 1H), 8.10 (d, J = 9.3 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 2.5 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 9.9 Hz, 1H), 6.82 (d, J = 9.0 Hz, 1H), 6.76 (d, J = 9.8 Hz, 1H), 6.65 (d, J = 2.5 Hz, 1H), 6.32 - 5.96 (m, 1H), 4.96 (s, 1H), 4.61 (dd, J = 8.2, 4.7 Hz, 1H),
 5 4.58 - 4.49 (m, 3H), 4.45 (dd, J = 14.2, 4.8 Hz, 1H), 4.37 (s, 1H), 4.21 (d, J = 9.9 Hz, 1H), 4.04 (d, J = 13.0 Hz, 2H), 3.84 (d, J = 13.2 Hz, 1H), 3.74 (d, J = 11.9 Hz, 1H), 3.67 (d, J = 11.5 Hz, 2H), 3.54 (s, 4H), 3.47 (s, 3H), 2.92 - 2.73 (m, 4H), 2.73 - 2.62 (m, 1H), 2.24 (s, 2H), 1.05 (d, J = 4.5 Hz, 7H), 1.01 (s, 3H), 0.92 (s, 3H).

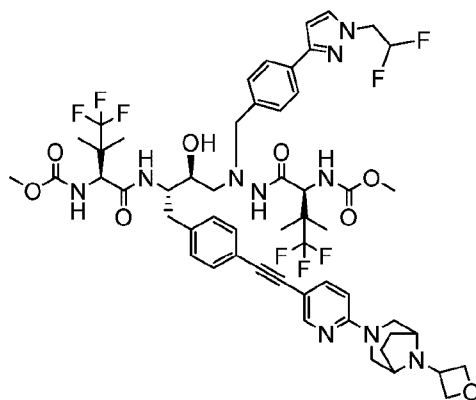


10

EXAMPLE 2

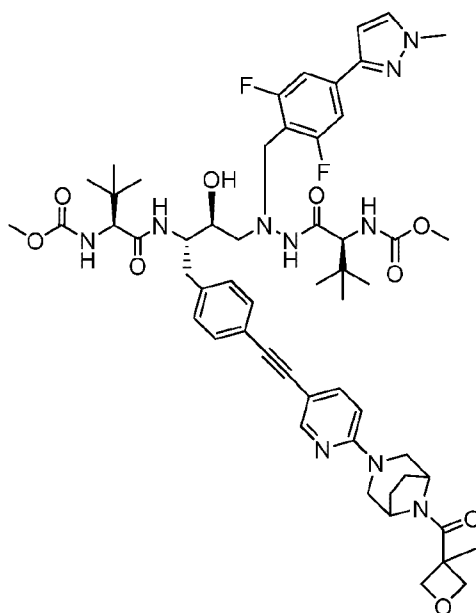
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-imidazol-4-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(4-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (2**)** Intermediates: **I3**, **P1**, and **S7**. MS (ESI) m/z 1102.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.53 (d, J = 0.8 Hz, 2H), 8.21 (d, J = 9.3 Hz, 1H), 8.17 (d, J = 1.2 Hz, 1H), 8.02 (d, J = 1.3 Hz, 1H), 7.59 (t, J = 59.9 Hz, 1H), 7.37 (dd, J = 19.9, 8.1 Hz, 5H), 7.23 (d, J = 7.9 Hz, 3H), 6.83 (d, J = 9.9 Hz, 1H), 4.96 (t, J = 7.6
 15 Hz, 3H), 4.81 (dd, J = 8.2, 5.0 Hz, 3H), 4.44 (d, J = 9.9 Hz, 1H), 4.12 (d, J = 19.4 Hz, 6H), 3.95 (d, J = 13.2 Hz, 1H), 3.75 (d, J = 10.1 Hz, 3H), 3.69 (d, J = 0.8 Hz, 4H), 3.65 (s, 4H), 3.46 (d, J = 14.4 Hz, 3H), 2.90 (d, J = 8.9 Hz, 2H), 2.79 (d, J = 8.9 Hz, 2H), 2.25 - 2.12 (m, 3H), 1.99 (d, J = 8.8 Hz, 2H), 1.14 (s, 4H), 1.10 (s, 4H), 0.86 (s, 12H).

20

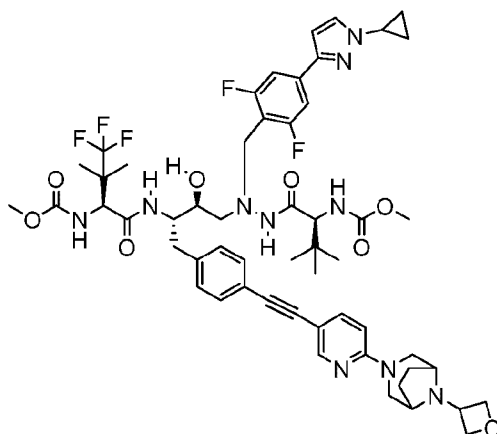


EXAMPLE 3

Methyl ((5S,10S,11S,14S)-8-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-10-hydroxy-15,15-dimethyl-11-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,8,12-tetraazahexadecan-14-yl)carbamate (3). Intermediates: **I2**, **P12**, and **S3**. MS (ESI) m/z 1133.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.29 (d, J = 2.2 Hz, 1H), 8.10 (d, J = 9.5 Hz, 1H), 7.69 (dd, J = 8.8, 2.3 Hz, 1H), 7.60 (d, J = 1.9 Hz, 1H), 7.53 (d, J = 7.9 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 9.7 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 10.0 Hz, 1H), 6.35 (d, J = 1.9 Hz, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.81 - 4.76 (m, 2H), 4.47 (td, J = 13.6, 4.3 Hz, 2H), 4.37 (dd, J = 19.3, 11.6 Hz, 2H), 4.25 (d, J = 9.7 Hz, 1H), 4.15 (s, 2H), 3.99 (d, J = 9.2 Hz, 2H), 3.74 (s, 1H), 3.68 (s, 3H), 3.60 (s, 3H), 3.39 (s, 1H), 3.36 (s, 1H), 2.90 (d, J = 9.0 Hz, 2H), 2.86 - 2.72 (m, 1H), 2.22 (d, J = 8.5 Hz, 2H), 2.07 (d, J = 8.6 Hz, 1H), 1.11 (s, 6H), 1.06 (s, 3H), 0.81 (s, 3H).

**EXAMPLE 4**

- methyl ((5S,8S,9S,14S)-5-(tert-butyl)-11-(2,6-difluoro-4-(1-methyl-1H-pyrazol-3-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-(((6-(8-(3-methyloxetane-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (4).** Intermediates: **11**, **P41**, and **S64**. MS (ESI) m/z 1053.33 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.21 (dd, $J = 2.2, 0.7$ Hz, 1H), 7.90 – 7.69 (m, 2H), 7.61 (d, $J = 2.3$ Hz, 1H), 7.33 (t, $J = 8.4$ Hz, 5H), 7.24 (d, $J = 8.0$ Hz, 2H), 6.98 (d, $J = 9.2$ Hz, 1H), 6.65 (d, $J = 2.3$ Hz, 1H), 5.06 (s, 1H), 4.93 (s, 1H), 4.41 (d, $J = 6.0$ Hz, 2H), 4.22 – 4.02 (m, 4H), 3.91 (d, $J = 13.2$ Hz, 6H), 3.79 – 3.54 (m, 9H), 3.20 (d, $J = 12.0$ Hz, 2H), 2.92 (h, $J = 5.7, 4.9$ Hz, 2H), 2.81 (d, $J = 7.9$ Hz, 2H), 2.08 – 1.80 (m, 6H), 1.69 (s, 3H), 0.87 (d, $J = 20.1$ Hz, 21H).

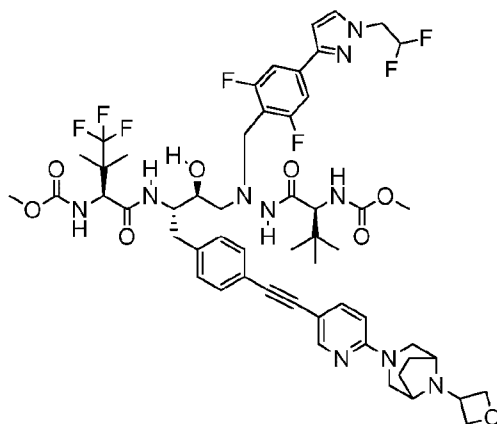


EXAMPLE 5

methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-

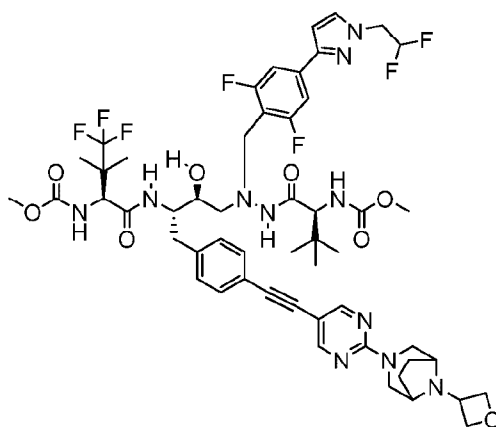
5 hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (5) Intermediates: **I3**, **P13**, and **S3**. MS (ESI) m/z 1091.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.20 (d, J = 2.3 Hz, 1H), 8.10 (d, J = 9.4 Hz, 1H), 7.60 (dt, J = 5.5, 2.7 Hz, 2H), 7.24 (t, J = 7.8 Hz, 4H), 7.12 (d, J = 8.1 Hz, 2H), 6.77 (d, J = 8.9 Hz, 1H), 6.71 (d, J = 9.9 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 4.95 - 4.85 (m, 2H), 4.71 (dd, J = 8.3, 5.0 Hz, 2H), 4.34 (d, J = 10.0 Hz, 1H), 4.26 (d, J = 14.3 Hz, 2H), 4.11 - 3.94 (m, 4H), 3.87 (s, 1H), 3.84 (s, 0H), 3.67 (s, 1H), 3.59 (s, 4H), 3.56 (s, 3H), 3.28 (d, J = 13.9 Hz, 2H), 2.80 (d, J = 9.1 Hz, 2H), 2.69 (d, J = 8.9 Hz, 2H), 2.21 - 2.04 (m, 2H), 1.98 (d, J = 8.6 Hz, 2H), 1.04 (s, 4H), 1.00 (s, 3H), 0.99 - 0.94 (m, 1H), 0.77 (s, 9H).

15



EXAMPLE 6

methyl ((5S,8S,9S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (6) Intermediates: **I3**, **P10**, and **S3**. MS (ESI) m/z 1115.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.20 (d, $J = 2.2$ Hz, 1H), 8.10 (d, $J = 9.3$ Hz, 1H), 7.64 (d, $J = 2.4$ Hz, 1H), 7.61 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.28 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 7.12 (d, $J = 8.1$ Hz, 2H), 6.77 (d, $J = 9.0$ Hz, 1H), 6.72 (d, $J = 9.9$ Hz, 0H), 6.65 (d, $J = 2.4$ Hz, 1H), 6.12 (tt, $J = 55.3, 4.0$ Hz, 1H), 4.87 (dd, $J = 8.3, 7.0$ Hz, 2H), 4.71 (dd, $J = 8.3, 5.0$ Hz, 2H), 4.54 - 4.42 (m, 2H), 4.38 - 4.31 (m, 1H), 4.26 (d, $J = 13.8$ Hz, 2H), 4.13 - 3.97 (m, 4H), 3.85 (s, 0H), 3.67 (s, 1H), 3.59 (s, 2H), 3.55 (s, 3H), 3.30 (s, 1H), 3.26 (s, 1H), 2.81 (d, $J = 9.3$ Hz, 2H), 2.70 (d, $J = 9.4$ Hz, 2H), 2.17 - 2.06 (m, 2H), 1.98 (d, $J = 8.6$ Hz, 2H), 1.05 (s, 3H), 1.01 (s, 3H), 0.77 (s, 9H).

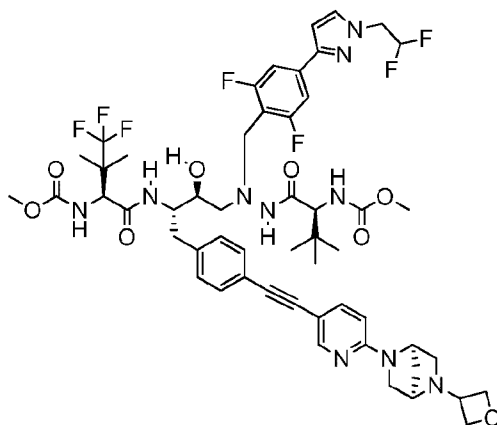


15

EXAMPLE 7

methyl ((5S,8S,9S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(4-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (7). Intermediates: **I3**, **P10**, and **S7**. MS (ESI) m/z 1117.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.44 (s, 2H), 8.11 (d, $J = 9.4$ Hz, 1H), 7.64 (d, $J = 2.4$ Hz, 1H), 7.26 (dd, $J = 14.0, 8.2$ Hz, 4H), 7.14 (d, $J = 8.1$ Hz, 2H), 6.73 (d, $J = 10.0$ Hz, 1H), 6.65 (d, $J = 2.5$ Hz, 1H), 6.12 (tt, $J = 55.3, 4.0$ Hz, 1H), 4.95 - 4.82 (m, 2H), 4.74 - 4.62 (m, 3H), 4.51 (td, $J = 14.3, 4.0$ Hz, 2H), 4.35 (d, $J = 9.9$ Hz, 1H), 4.02 (d, $J =$

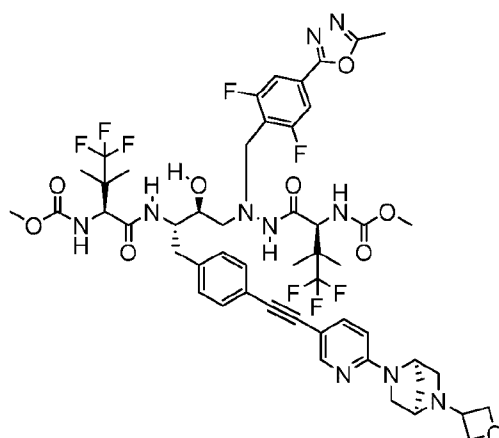
19.0 Hz, 4H), 3.86 (d, J = 13.2 Hz, 1H), 3.67 (s, 1H), 3.59 (s, 3H), 3.55 (s, 3H), 3.37 (d, J = 14.5 Hz, 2H), 2.81 (d, J = 8.9 Hz, 2H), 2.70 (d, J = 9.3 Hz, 2H), 2.23 - 2.02 (m, 2H), 1.98 - 1.83 (m, 2H), 1.04 (s, 3H), 1.01 (s, 3H), 0.77 (s, 9H).



5

EXAMPLE 8

methyl ((5S,8S,9S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(4-((6-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (8). Intermediates: **I3**, **P10**, and **S6**. MS (ESI) m/z 1101.6 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.16 (d, J = 2.2 Hz, 1H), 8.08 (d, J = 9.4 Hz, 1H), 7.64 (d, J = 2.4 Hz, 1H), 7.61 (dd, J = 8.8, 2.2 Hz, 1H), 7.25 (dd, J = 21.0, 8.1 Hz, 3H), 7.12 (d, J = 8.0 Hz, 2H), 6.70 (d, J = 10.3 Hz, 0H), 6.64 (d, J = 2.4 Hz, 1H), 6.58 (d, J = 8.8 Hz, 1H), 6.12 (tt, J = 55.2, 3.9 Hz, 1H), 4.96 (s, 1H), 4.91 - 4.82 (m, 1H), 4.61 (dd, J = 8.4, 4.6 Hz, 1H), 4.57 - 4.42 (m, 3H), 4.41 (s, 1H), 4.35 (d, J = 6.5 Hz, 1H), 4.02 (d, J = 13.2 Hz, 2H), 3.87 (d, J = 13.2 Hz, 1H), 3.72 - 3.61 (m, 3H), 3.59 (s, 3H), 3.55 (s, 2H), 2.80 (d, J = 8.7 Hz, 1H), 2.70 (d, J = 9.5 Hz, 2H), 2.24 (s, 2H), 1.05 (s, 3H), 1.01 (s, 3H), 0.77 (s, 8H).

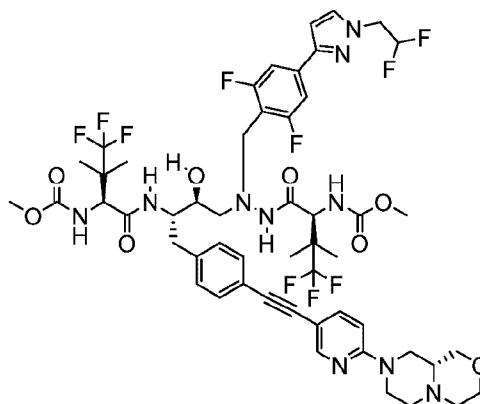


EXAMPLE 9

5 methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(5-methyl-1,3,4-oxadiazol-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trifluoro-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (9).

Intermediates: **I2**, **P34**, and **S6**. MS (ESI) m/z 1101.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.16 (d, J = 2.1 Hz, 1H), 8.10 (d, J = 9.4 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.48 (d, J = 7.1 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.76 (d, J = 10.1 Hz, 1H), 6.57 (d, J = 8.8 Hz, 1H), 4.96 (s, 1H), 4.61 (s, 1H), 4.49 (t, J = 8.9 Hz, 1H), 4.41 (s, 1H), 4.35 (d, J = 9.7 Hz, 1H), 4.18 (d, J = 9.9 Hz, 1H), 4.09 (d, J = 13.1 Hz, 1H), 3.87 (d, J = 13.1 Hz, 1H), 3.77 - 3.55 (m, 8H), 2.82 (d, J = 8.5 Hz, 3H), 2.71 (d, J = 10.1 Hz, 1H), 2.54 (s, 3H), 2.23 (s, 2H), 1.05 (d, J = 7.7 Hz, 9H), 0.92 (s, 3H).

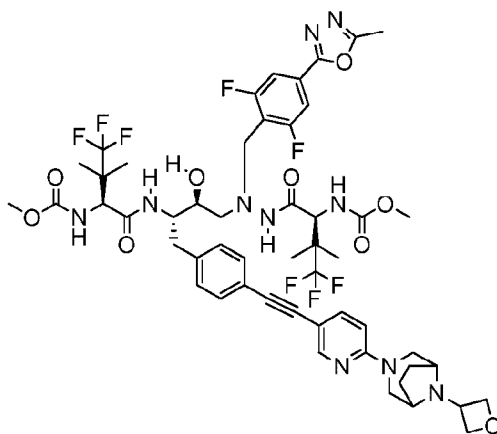
15



EXAMPLE 10

Methyl ((5S,8S,9S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-8-(4-((6-((R)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)pyridin-3-yl)ethynyl)benzyl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (10).

Intermediates: **I2**, **P10**, and **S8**. MS (ESI) m/z 1143.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.26 - 8.19 (m, 1H), 8.10 (d, J = 9.4 Hz, 1H), 7.65 (d, J = 2.5 Hz, 1H), 7.61 (dd, J = 8.9, 2.3 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 6.86 (d, J = 8.9 Hz, 1H), 6.72 (d, J = 10.0 Hz, 1H), 6.66 (d, J = 2.4 Hz, 1H), 6.30 - 5.97 (m, 1H), 4.51 (td, J = 14.2, 3.9 Hz, 3H), 4.35 (d, J = 9.7 Hz, 1H), 4.22 (d, J = 10.0 Hz, 1H), 4.04 (d, J = 12.4 Hz, 4H), 3.60 (s, 3H), 3.57 (s, 3H), 3.48 (d, J = 11.0 Hz, 1H), 2.89 - 2.61 (m, 5H), 1.08 (s, 4H), 1.05 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H).

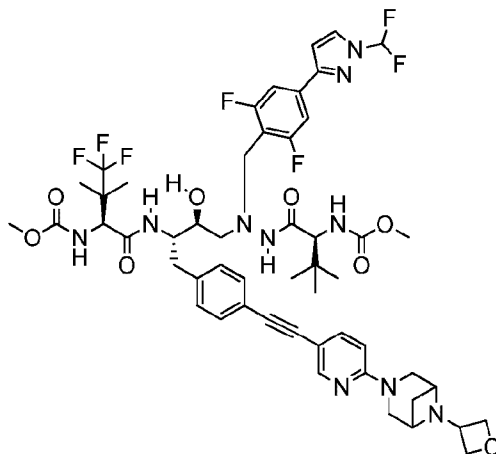
**EXAMPLE 11**

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(5-methyl-1,3,4-oxadiazol-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (11). Intermediates: **I2**, **P34**, and **S3**. MS

(ESI) m/z 1121.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.20 (d, J = 2.3 Hz, 1H), 8.08 (d, J = 9.4 Hz, 1H), 7.60 (dd, J = 8.9, 2.3 Hz, 1H), 7.48 (d, J = 7.1 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 10.5 Hz, 1H), 6.77 (d, J = 9.0 Hz, 1H), 6.73 (d, J = 9.9 Hz, 1H), 4.93 - 4.82 (m, 2H), 4.74 - 4.63 (m, 2H), 4.34 (d, J = 9.9 Hz, 1H), 4.26 (d, J = 13.5 Hz,

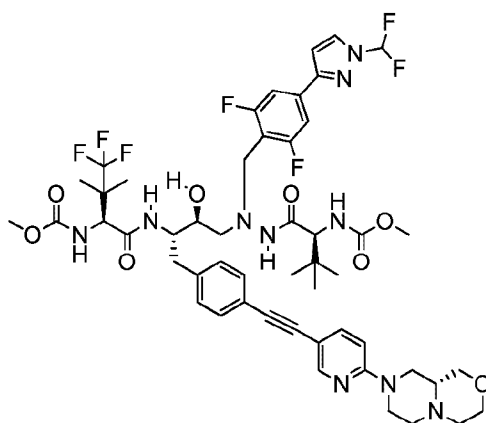
1H), 4.18 (d, J = 10.0 Hz, 1H), 4.09 (d, J = 17.9 Hz, 4H), 3.88 (d, J = 13.1 Hz, 1H), 3.64 (s, 1H), 3.60 (d, J = 2.9 Hz, 6H), 3.28 (d, J = 13.8 Hz, 2H), 2.82 (d, J = 8.6 Hz, 3H), 2.75 - 2.62 (m, 1H), 2.54 (s, 3H), 2.22 - 2.06 (m, 2H), 1.98 (d, J = 8.6 Hz, 2H), 1.06 (s, 6H), 1.04 (s, 3H), 0.93 (s, 3H).

5

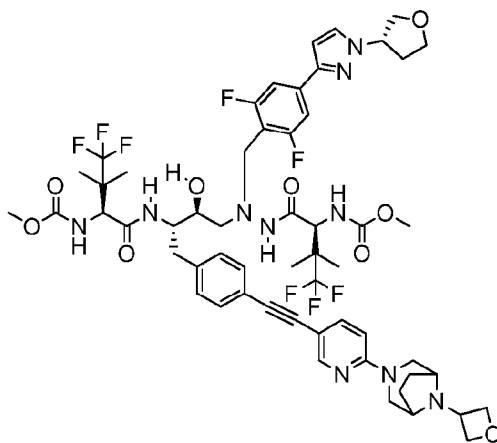


EXAMPLE 12

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(((6-(6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (12). Intermediates: **I3**, **P4**, and **S4**. MS (ESI) m/z 1087.8 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.33 (s, 1H), 8.15 (d, J = 9.4 Hz, 1H), 8.10 (d, J = 2.8 Hz, 1H), 7.78 - 7.71 (m, 1H), 7.52 (t, J = 59.9 Hz, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.8 Hz, 3H), 7.22 (d, J = 7.9 Hz, 3H), 6.93 (d, J = 2.7 Hz, 1H), 6.78 (d, J = 9.2 Hz, 2H), 4.70 - 4.57 (m, 2H), 4.44 (d, J = 9.7 Hz, 1H), 4.13 (d, J = 12.4 Hz, 3H), 3.97 (d, J = 13.0 Hz, 1H), 3.76 (s, 1H), 3.69 (s, 4H), 3.65 (s, 3H), 2.90 (d, J = 8.7 Hz, 2H), 2.80 (d, J = 11.1 Hz, 2H), 2.11 (d, J = 10.6 Hz, 1H), 1.39 - 1.23 (m, 2H), 1.15 (s, 4H), 1.11 (s, 4H), 0.86 (s, 11H).

**EXAMPLE 13**

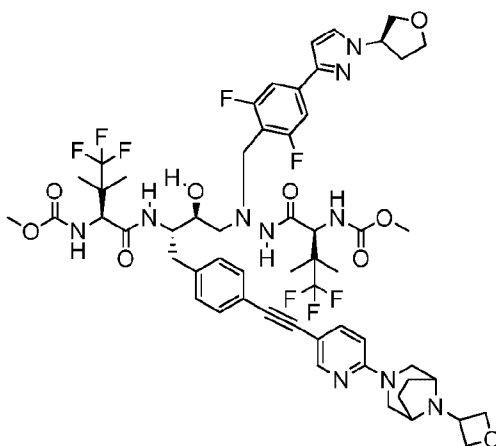
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-8-(4-(((6-((R)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)pyridin-3-yl)ethynyl)benzyl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (13). Intermediates: **I3**, **P4**, and **S8**. MS (ESI) m/z 1073.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.30 (d, $J = 2.2$ Hz, 1H), 8.19 (d, $J = 9.3$ Hz, 1H), 8.10 (d, $J = 2.7$ Hz, 1H), 7.75 - 7.59 (m, 2H), 7.56 (dd, $J = 7.4, 3.4$ Hz, 1H), 7.53 (t, $J = 59.8$ Hz, 2H), 7.45 (d, $J = 8.2$ Hz, 3H), 7.32 (d, $J = 7.9$ Hz, 3H), 7.22 (d, $J = 8.1$ Hz, 3H), 7.03 - 6.88 (m, 3H), 6.82 (d, $J = 10.0$ Hz, 1H), 4.62 (dd, $J = 22.7, 13.0$ Hz, 2H), 4.44 (d, $J = 9.7$ Hz, 1H), 4.12 (d, $J = 12.2$ Hz, 6H), 3.97 (d, $J = 13.1$ Hz, 2H), 3.85 (t, $J = 12.6$ Hz, 1H), 3.76 (s, 2H), 3.69 (s, 4H), 3.59 (d, $J = 10.8$ Hz, 2H), 3.01 - 2.70 (m, 6H), 1.14 (s, 4H), 1.11 (s, 4H), 0.86 (s, 12H).



EXAMPLE 14

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(1-((S)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (14).

Intermediates: **I2**, **P17**, and **S3**. MS (ESI) m/z 1176.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.20 (d, J = 2.3 Hz, 1H), 8.11 (d, J = 9.3 Hz, 1H), 7.68 - 7.58 (m, 2H), 7.25 (dd, J = 13.9, 8.3 Hz, 4H), 7.12 (d, J = 8.0 Hz, 2H), 6.75 (dd, J = 17.1, 9.4 Hz, 2H), 6.59 (d, J = 2.4 Hz, 1H), 4.97 (dq, J = 8.2, 3.8 Hz, 1H), 4.87 (t, J = 7.6 Hz, 3H), 4.71 (dd, J = 8.3, 5.0 Hz, 3H), 4.52 - 4.32 (m, 1H), 4.32 - 4.18 (m, 3H), 4.17 - 3.99 (m, 6H), 3.97 (d, J = 4.7 Hz, 2H), 3.84 (td, J = 8.3, 5.4 Hz, 2H), 3.58 (d, J = 9.5 Hz, 8H), 3.27 (d, J = 13.9 Hz, 3H), 2.80 - 2.52 (m, 4H), 2.45 - 2.33 (m, 1H), 2.33 - 2.23 (m, 1H), 2.13 (d, J = 10.7 Hz, 2H), 2.03 - 1.92 (m, 2H), 1.07 (s, 4H), 1.05 (s, 3H), 1.00 (s, 3H), 0.94 (s, 3H).

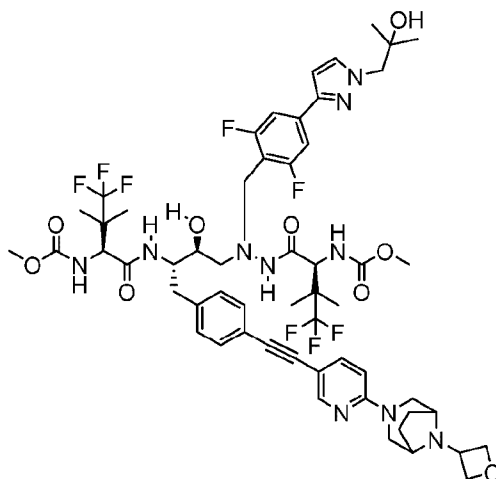
**EXAMPLE 15**

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (15).

Intermediates: **I2**, **P18**, and **S3**. MS (ESI) m/z 1176.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.19 (s, 1H), 8.11 (d, J = 9.4 Hz, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.25 (dd, J = 14.4, 8.2 Hz, 4H), 7.12 (d, J = 8.0 Hz, 2H), 6.74 (t, J = 10.2 Hz, 2H), 6.59 (d, J = 2.4 Hz, 1H), 4.98 (dd, J = 8.3, 3.9 Hz, 1H), 4.69 (t, J = 6.7 Hz, 2H), 4.35 (d, J = 9.9 Hz, 1H),

4.22 (d, J = 10.0 Hz, 1H), 4.03 (dd, J = 14.5, 7.1 Hz, 3H), 3.97 (d, J = 4.7 Hz, 2H), 3.90 - 3.79 (m, 2H), 3.63 (s, 1H), 3.58 (d, J = 9.2 Hz, 6H), 2.81 (d, J = 7.8 Hz, 2H), 2.68 (d, J = 10.0 Hz, 1H), 2.49 - 2.33 (m, 1H), 2.33 - 2.21 (m, 1H), 2.10 (s, 1H), 1.94 (s, 0H), 1.07 (s, 3H), 1.05 (s, 3H), 1.00 (s, 3H), 0.94 (s, 3H).

5

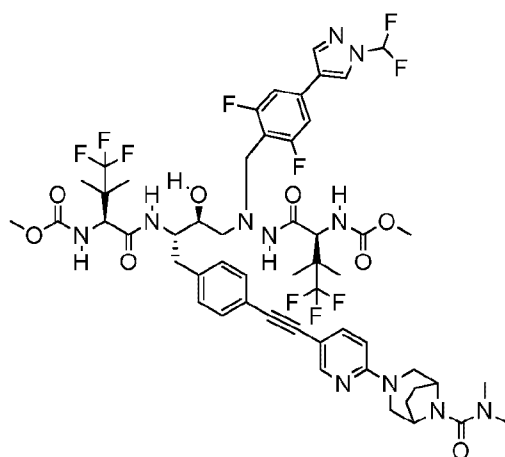


EXAMPLE 16

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-4-(((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (16).

Intermediates: **I2**, **P19**, and **S3**. MS (ESI) m/z 1177.2 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.20 (s, 1H), 8.10 (d, J = 9.2 Hz, 1H), 7.61 (s, 1H), 7.59 (d, J = 2.3 Hz, 2H), 7.25 (dd, J = 12.2, 8.1 Hz, 4H), 7.12 (d, J = 8.0 Hz, 2H), 6.77 (d, J = 9.0 Hz, 1H), 6.72 (d, J = 10.2 Hz, 1H), 6.60 (d, J = 2.4 Hz, 1H), 4.87 (t, J = 7.6 Hz, 3H), 4.71 (dd, J = 8.3, 5.0 Hz, 2H), 4.35 (d, J = 9.9 Hz, 1H), 4.30 - 4.13 (m, 2H), 4.03 (d, J = 12.6 Hz, 3H), 3.84 (d, J = 13.3 Hz, 1H), 3.58 (d, J = 8.2 Hz, 5H), 3.28 (d, J = 13.9 Hz, 2H), 2.81 (d, J = 7.8 Hz, 2H), 2.72 (d, J = 15.2 Hz, 1H), 2.12 (s, 1H), 1.98 (d, J = 8.6 Hz, 2H), 1.10 (s, 6H), 1.07 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H).

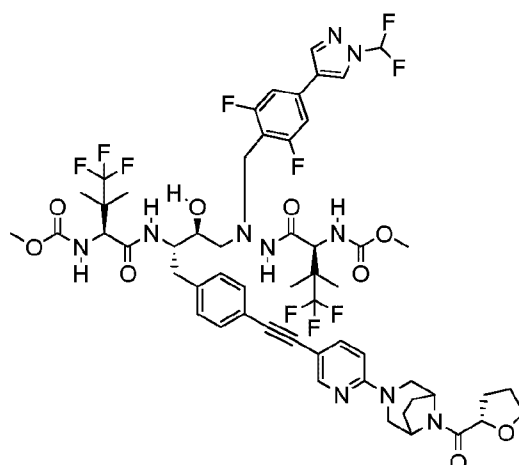
20



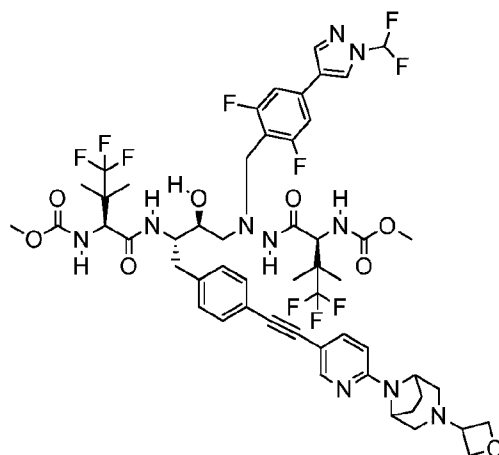
EXAMPLE 17

**Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-8-
 (4-((6-(8-(dimethylcarbamoyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-
 5-yl)ethynyl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-
 trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (17).**

Intermediates: **I2**, **P7**, and **S24**. MS (ESI) m/z 1177.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol-
 d4) δ 8.53 (d, $J = 0.7$ Hz, 1H), 8.22 - 8.13 (m, 2H), 8.11 (s, 1H), 7.86 (dd, $J = 9.3, 2.2$ Hz, 1H),
 7.50 (s, 1H), 7.40 - 7.30 (m, 2H), 7.23 (dd, $J = 8.2, 5.7$ Hz, 4H), 7.17 (d, $J = 9.9$ Hz, 1H), 7.10
 10 (d, $J = 9.3$ Hz, 1H), 6.81 (d, $J = 9.9$ Hz, 1H), 4.50 - 4.37 (m, 1H), 4.35 - 4.23 (m, 3H), 4.12 (t, J
 = 11.1 Hz, 2H), 4.00 - 3.87 (m, 3H), 3.66 (d, $J = 10.3$ Hz, 7H), 3.43 - 3.33 (m, 2H), 2.96 (s, 6H),
 2.94 - 2.69 (m, 2H), 1.96 (t, $J = 5.3$ Hz, 2H), 1.78 (t, $J = 6.9$ Hz, 2H), 1.26 - 1.07 (m, 9H), 1.02
 (s, 3H).

**EXAMPLE 18**

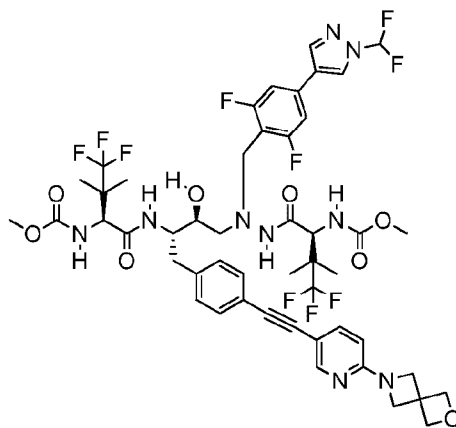
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-(4-((6-(8-((S)-tetrahydrofuran-2-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (18). Intermediates: **I2**, **P7**, and **S25**. MS (ESI) m/z 1177.2 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.44 (s, 1H), 8.13 - 8.05 (m, 2H), 8.03 (s, 1H), 7.68 (t, J = 8.5 Hz, 1H), 7.41 (s, 1H), 7.31 - 7.22 (m, 2H), 7.20 - 7.05 (m, 5H), 6.96 - 6.84 (m, 1H), 6.72 (d, J = 10.0 Hz, 1H), 4.75 - 4.65 (m, 5H), 4.60 (dd, J = 7.6, 6.2 Hz, 2H), 4.40 - 4.26 (m, 1H), 4.25 - 4.12 (m, 1H), 4.10 - 3.87 (m, 4H), 3.87 - 3.71 (m, 3H), 3.58 (d, J = 10.7 Hz, 6H), 3.17 - 2.96 (m, 2H), 2.89 - 2.59 (m, 4H), 2.19 - 1.93 (m, 2H), 1.93 - 1.67 (m, 4H), 1.15 - 0.96 (m, 9H), 0.94 (s, 3H).



EXAMPLE 19

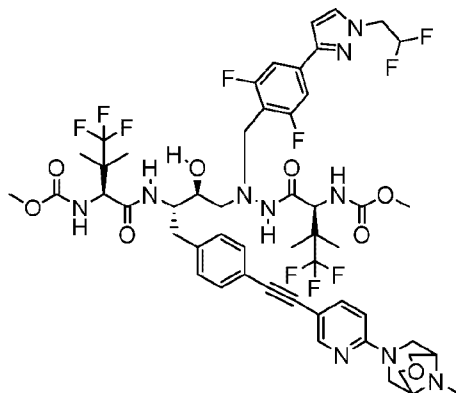
methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(((6-(3-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (19).

Intermediates: **I2**, **P7**, and **S26**. MS (ESI) m/z 1177.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.54 (d, J = 0.7 Hz, 1H), 8.26 - 8.22 (m, 1H), 8.17 (d, J = 9.4 Hz, 1H), 8.12 (s, 1H), 7.78 (d, J = 8.9 Hz, 1H), 7.51 (s, 1H), 7.39 - 7.32 (m, 2H), 7.24 (t, J = 8.3 Hz, 4H), 7.17 (d, J = 9.8 Hz, 1H), 7.01 (d, J = 9.0 Hz, 1H), 6.81 (d, J = 9.9 Hz, 1H), 4.80 (ddtd, J = 4.5, 2.0, 1.0, 0.5 Hz, 1H), 4.76 - 4.69 (m, 4H), 4.50 - 4.37 (m, 1H), 4.36 - 4.25 (m, 1H), 4.13 (t, J = 10.7 Hz, 3H), 3.93 (d, J = 13.2 Hz, 1H), 3.68 (d, J = 10.5 Hz, 6H), 2.97 - 2.66 (m, 6H), 2.33 - 2.10 (m, 3H), 1.26 - 1.08 (m, 9H), 1.03 (s, 3H).

**EXAMPLE 20**

methyl ((5S,8S,9S,14S)-8-(4-(((6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-3-yl)ethynyl)benzyl)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (20).

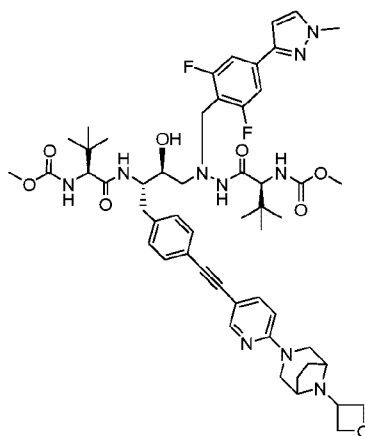
Intermediates: **I2**, **P7**, and **S27**. MS (ESI) m/z 1086.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.54 (s, 1H), 8.17 (d, J = 9.2 Hz, 1H), 8.12 (s, 1H), 8.08 (d, J = 1.9 Hz, 1H), 7.93 (dd, J = 9.4, 2.0 Hz, 1H), 7.69 - 7.60 (m, 1H), 7.56 (dd, J = 7.2, 3.3 Hz, 0H), 7.51 (s, 0H), 7.40 - 7.33 (m, 2H), 7.25 (d, J = 8.0 Hz, 4H), 7.17 (d, J = 9.9 Hz, 1H), 6.83 (d, J = 9.3 Hz, 1H), 4.86 (s, 4H), 4.49 (s, 4H), 4.43 (d, J = 3.7 Hz, 1H), 4.36 - 4.25 (m, 1H), 4.24 - 4.05 (m, 2H), 3.92 (d, J = 13.1 Hz, 1H), 3.67 (d, J = 7.6 Hz, 7H), 2.99 - 2.70 (m, 4H), 1.23 - 1.06 (m, 9H), 1.03 (s, 3H).

**EXAMPLE 21**

methyl ((5S,8S,9S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-

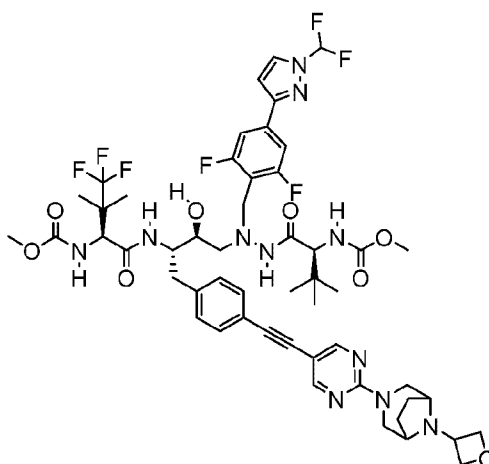
16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(((6-(9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (21).

Intermediates: **12**, **P10**, and **S2**. MS (ESI) m/z 1143.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.18 (d, $J = 2.3$ Hz, 1H), 8.06 (d, $J = 9.3$ Hz, 1H), 7.64 (d, $J = 2.5$ Hz, 1H), 7.58 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.28 (d, $J = 8.5$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 7.12 (d, $J = 8.1$ Hz, 2H), 7.02 (d, $J = 9.7$ Hz, 1H), 6.77 (d, $J = 9.0$ Hz, 1H), 6.71 - 6.61 (m, 2H), 6.12 (tt, $J = 55.4, 4.0$ Hz, 1H), 4.50 (td, $J = 14.3, 3.9$ Hz, 2H), 4.34 (d, $J = 9.6$ Hz, 1H), 4.29 - 4.18 (m, 1H), 4.04 (d, $J = 13.0$ Hz, 6H), 3.84 (d, $J = 13.2$ Hz, 1H), 3.63 (s, 3H), 3.56 (s, 3H), 3.50 (s, 2H), 3.10 (s, 3H), 2.81 (d, $J = 8.1$ Hz, 2H), 2.69 (d, $J = 9.4$ Hz, 1H), 1.07 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H).



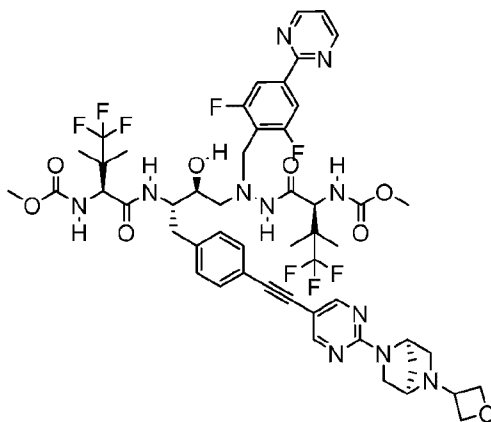
EXAMPLE 22

Methyl ((5S,8S,9S,14S)-5-(tert-butyl)-11-(2,6-difluoro-4-(1-methyl-1H-pyrazol-3-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-(((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (22). Intermediates **11**, **P41**, and **S3**. MS (ESI) m/z 1011.29 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.30 (d, $J = 2.2$ Hz, 1H), 7.70 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.61 (d, $J = 2.3$ Hz, 1H), 7.33 (d, $J = 7.7$ Hz, 5H), 7.23 (d, $J = 7.8$ Hz, 2H), 6.86 (d, $J = 8.9$ Hz, 1H), 6.65 (d, $J = 2.3$ Hz, 1H), 4.96 (t, $J = 7.6$ Hz, 2H), 4.82 – 4.77 (m, 2H), 4.35 (d, $J = 13.8$ Hz, 2H), 4.13 (d, $J = 13.4$ Hz, 4H), 3.93 (s, 6H), 3.67 (d, $J = 6.4$ Hz, 8H), 3.38 (d, $J = 13.9$ Hz, 2H), 3.00 – 2.77 (m, 5H), 2.31 – 2.20 (m, 2H), 2.14 – 2.04 (m, 2H), 0.87 (d, $J = 20.7$ Hz, 21H).

**EXAMPLE 23**

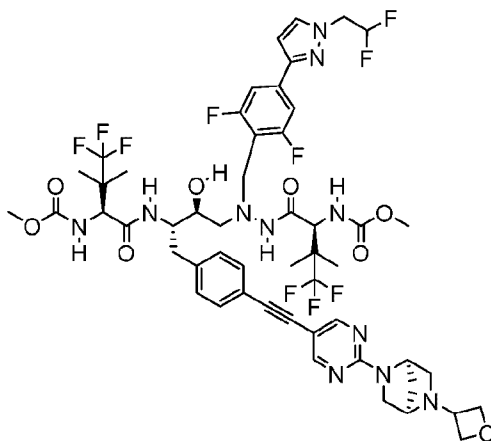
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (23). Intermediates: **I3**, **P4**, and **S7**. MS (ESI) m/z 1102.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.53 (s, 2H), 8.20 (d, $J = 9.4$ Hz, 1H), 8.11 (d, $J = 2.7$ Hz, 1H), 7.53 (t, $J = 59.9, 59.4$ Hz, 1H), 7.45 (d, $J = 8.2$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 8.2$ Hz, 2H), 6.94 (d, $J = 2.8$ Hz, 1H), 6.83 (d, $J = 9.9$ Hz, 1H), 5.03 - 4.92 (m, 2H), 4.83 - 4.76 (m, 2H), 4.44 (d, $J = 10.0$ Hz, 1H), 4.16 - 4.05 (m, 2H), 3.97 (d, $J = 13.2$ Hz, 1H), 3.85 - 3.71 (m, 1H), 3.69 (s, 3H), 3.65 (s, 3H), 3.54 - 3.39 (m, 2H), 2.96 - 2.72

(m, 3H), 2.27 - 2.13 (m, 2H), 2.04 - 1.91 (m, 2H), 1.14 (s, 3H), 1.11 (s, 3H), 0.86 (s, 9H).



EXAMPLE 24

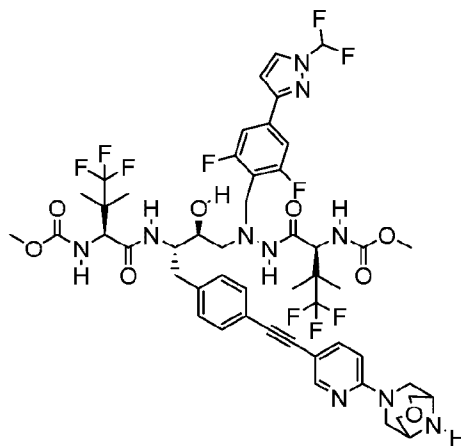
- 5 **Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyrimidin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((2-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (24).** Intermediates: **I2**, **P16**, and **S29**. MS (ESI) m/z 1104.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.87 (d, J = 4.9 Hz, 2H), 8.52 (s, 2H), 8.19 (d, J = 9.5 Hz, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.41 (t, J = 4.9 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 10.1 Hz, 1H), 6.82 (d, J = 10.1 Hz, 1H), 5.18 (s, 1H), 4.99 - 4.90 (m, 2H), 4.64 - 4.55 (m, 1H), 4.44 (d, J = 10.0 Hz, 1H), 4.30 (d, J = 10.0 Hz, 1H), 4.24 - 4.10 (m, 2H), 3.98 (d, J = 13.0 Hz, 1H), 3.90 (d, J = 12.5 Hz, 1H), 3.85 - 3.72 (m, 3H), 3.69 (s, 3H), 3.67 (s, 3H), 2.96 - 2.74 (m, 4H), 2.33 (s, 2H), 1.15 (s, 6H), 1.11 (s, 3H), 1.02 (s, 3H).



EXAMPLE 25

Methyl ((5S,8S,9S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-(((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (25).

Intermediates: **I2**, **P10**, and **S29**. MS (ESI) m/z 1156.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 2H), 8.18 (d, J = 9.3 Hz, 1H), 7.37 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 9.9 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.22 (tt, J = 55.5, 4.0 Hz, 1H), 5.18 (s, 1H), 5.01 - 4.90 (m, 2H), 4.72 (s, 1H), 4.60 (td, J = 14.1, 3.7 Hz, 4H), 4.52 (s, 0H), 4.44 (d, J = 9.9 Hz, 1H), 4.31 (d, J = 10.0 Hz, 1H), 4.20 - 4.07 (m, 2H), 3.98 - 3.86 (m, 2H), 3.81 (d, J = 12.8 Hz, 1H), 3.76 - 3.71 (m, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 3.00 - 2.71 (m, 4H), 2.34 (s, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H).



15

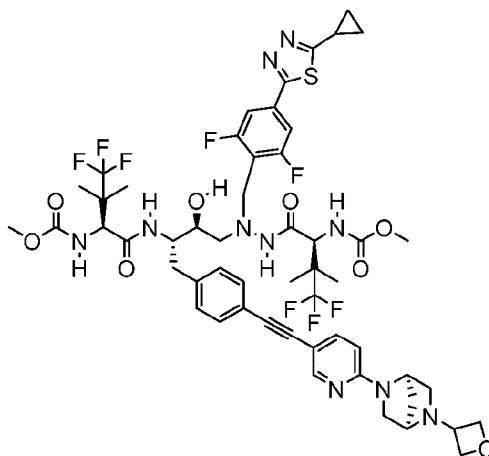
EXAMPLE 26

Methyl ((5S,8S,9S,14S)-8-((6-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)pyridin-3-yl)ethynyl)benzyl)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (26).

Intermediates: **I2**, **P4**, and **S28**. MS (ESI) m/z 1115.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.17 (d, J = 2.3 Hz, 1H), 8.07 (d, J = 9.4 Hz, 1H), 8.01 (d, J = 2.8 Hz, 1H), 7.56 (dd, J = 8.8, 2.4 Hz, 1H), 7.44 (t, J = 59.9 Hz, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 6.84 (d, J = 2.7 Hz, 1H), 6.78 (d, J = 9.1 Hz, 1H), 6.69 (d, J = 10.0 Hz,

1H), 4.70 - 4.61 (m, 2H), 4.34 (d, J = 9.8 Hz, 1H), 4.21 (d, J = 10.0 Hz, 1H), 4.08 - 4.00 (m, 4H), 3.94 (d, J = 13.0 Hz, 2H), 3.85 (d, J = 13.1 Hz, 1H), 3.64 (s, 1H), 3.60 (s, 3H), 3.58 - 3.54 (m, 4H), 3.42 (d, J = 14.4 Hz, 3H), 2.85 - 2.62 (m, 4H), 1.07 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H).

5

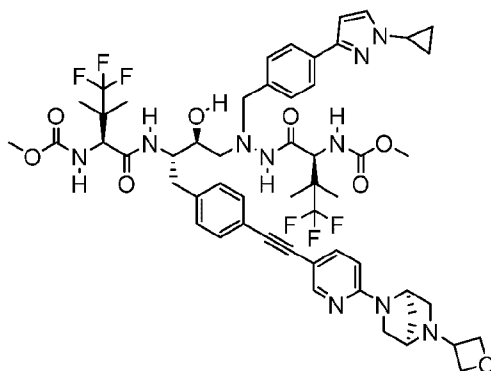


EXAMPLE 27

Methyl ((5S,8S,9S,14S)-11-(4-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(((6-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (27).

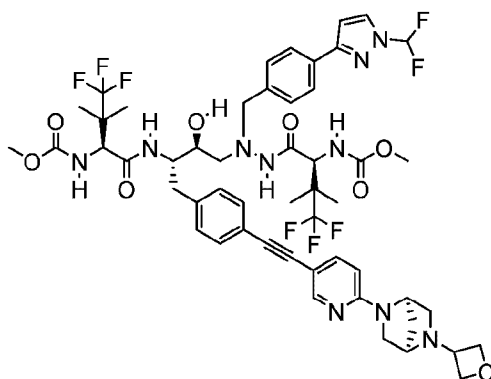
Intermediates: **I2**, **P3**, and **S6**. MS (ESI) m/z 1149.3 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.16 (d, J = 2.2 Hz, 1H), 8.06 (d, J = 9.4 Hz, 1H), 7.60 (dd, J = 8.8, 2.3 Hz, 1H), 7.42 (d, J = 7.5 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 10.1 Hz, 1H), 6.71 (d, J = 10.0 Hz, 1H), 6.56 (d, J = 8.8 Hz, 1H), 4.96 (s, 1H), 4.92 - 4.78 (m, 2H), 4.61 (s, 1H), 4.55 - 4.44 (m, 1H), 4.41 (s, 1H), 4.34 (d, J = 9.8 Hz, 1H), 4.19 (d, J = 10.0 Hz, 1H), 4.12 - 4.01 (m, 2H), 3.87 (d, J = 13.1 Hz, 1H), 3.72 - 3.61 (m, 2H), 3.60 (s, 3H), 3.58 (s, 3H), 2.89 - 2.75 (m, 3H), 2.73 - 2.61 (m, 1H), 2.43 (ddd, J = 13.1, 8.5, 4.9 Hz, 1H), 2.23 (s, 2H), 1.27 - 1.18 (m, 2H), 1.10 - 1.01 (m, 11H), 0.93 (s, 3H).

20

**EXAMPLE 28**

Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (28). Intermediates: **I2**, **P21**, and **S6**. MS (ESI) m/z 1095.8 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.16 (d, J = 2.2 Hz, 1H), 8.02 (d, J = 9.5 Hz, 1H), 7.62 - 7.57 (m, 3H), 7.56 (d, J = 2.4 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 7.04 (s, 1H), 6.67 (d, J = 9.7 Hz, 1H), 6.56 (d, J = 8.8 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 4.96 (s, 1H), 4.89 - 4.83 (m, 1H), 4.84 - 4.78 (m, 1H), 4.65 - 4.54 (m, 1H), 4.54 - 4.44 (m, 2H), 4.41 (s, 1H), 4.30 (d, J = 9.9 Hz, 1H), 4.16 (d, J = 9.7 Hz, 1H), 4.12 - 4.00 (m, 1H), 3.88 (d, J = 13.2 Hz, 1H), 3.78 (d, J = 13.5 Hz, 1H), 3.73 - 3.60 (m, 2H), 3.60 - 3.53 (m, 4H), 3.51 (s, 3H), 2.87 - 2.76 (m, 2H), 2.76 - 2.59 (m, 2H), 2.23 (s, 2H), 1.07 - 0.94 (m, 10H), 0.92 (s, 3H), 0.72 (s, 3H).

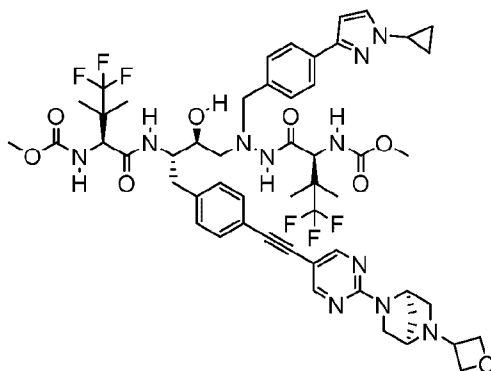
15



EXAMPLE 29

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(((6-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (29).

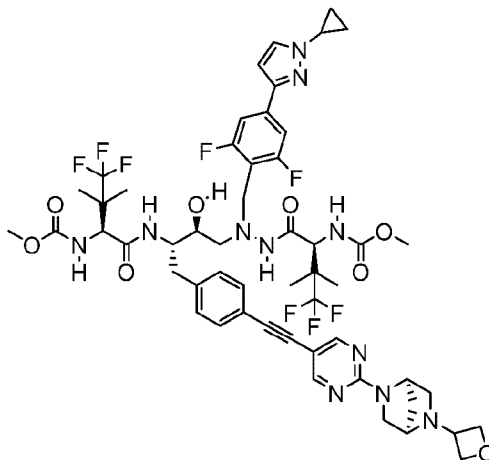
Intermediates: **I2**, **P6**, and **S6**. MS (ESI) m/z 1105.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.25 (d, $J = 2.2$ Hz, 1H), 8.11 (d, $J = 9.3$ Hz, 1H), 8.05 (d, $J = 2.7$ Hz, 1H), 7.78 (d, $J = 8.1$ Hz, 2H), 7.69 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.49 (t, $J = 59.7$ Hz, 1H), 7.45 (d, $J = 8.1$ Hz, 2H), 7.32 (d, $J = 7.9$ Hz, 2H), 7.22 (d, $J = 8.1$ Hz, 2H), 7.12 (d, $J = 9.4$ Hz, 1H), 6.86 (d, $J = 2.7$ Hz, 1H), 6.77 (d, $J = 9.9$ Hz, 1H), 6.66 (d, $J = 8.7$ Hz, 1H), 5.05 (s, 1H), 4.95 (dd, $J = 8.4, 6.5$ Hz, 1H), 4.93 - 4.87 (m, 1H), 4.70 (dd, $J = 8.5, 4.6$ Hz, 1H), 4.66 - 4.53 (m, 2H), 4.50 (s, 1H), 4.40 (d, $J = 9.9$ Hz, 1H), 4.24 (d, $J = 9.8$ Hz, 1H), 4.21 - 4.12 (m, 1H), 4.01 (d, $J = 13.2$ Hz, 1H), 3.88 (d, $J = 13.2$ Hz, 1H), 3.82 - 3.69 (m, 2H), 3.68 (s, 3H), 3.59 (s, 3H), 2.96 - 2.66 (m, 4H), 2.33 (s, 2H), 1.12 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 0.83 (s, 3H).

**EXAMPLE 30**

methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((2-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (30). Intermediates: **I2**, **P21**, and **S29**. MS (ESI) m/z 1096.7 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.51 (s, 2H), 8.10 (d, $J = 9.0$ Hz, 1H), 7.68 (d, $J = 8.0$ Hz, 2H), 7.65 (d, $J = 2.4$ Hz, 1H), 7.40 (d, $J = 7.9$ Hz, 2H), 7.34 (d, $J = 7.8$ Hz, 2H), 7.22 (d, $J = 7.9$ Hz, 2H), 6.76 (d, $J = 10.1$ Hz, 1H), 6.56 (d, $J = 2.4$ Hz, 1H), 5.18 (s, 1H), 4.93 (dt, $J = 20.6, 7.3$ Hz, 1H), 4.72 (s, 1H), 4.65 - 4.55 (m, 1H), 4.51 (s, 0H), 4.40 (d, $J =$

7.8 Hz, 1H), 4.25 (d, J = 7.8 Hz, 1H), 4.15 (s, 1H), 4.02 - 3.78 (m, 3H), 3.67 (s, 3H), 3.66 (d, J = 3.8 Hz, 1H), 3.59 (s, 3H), 2.94 - 2.67 (m, 4H), 2.41 - 2.30 (m, 2H), 2.05 - 1.99 (m, 1H), 1.93 (s, 1H), 1.15 - 1.04 (m, 10H), 1.01 (s, 3H), 0.81 (s, 3H).

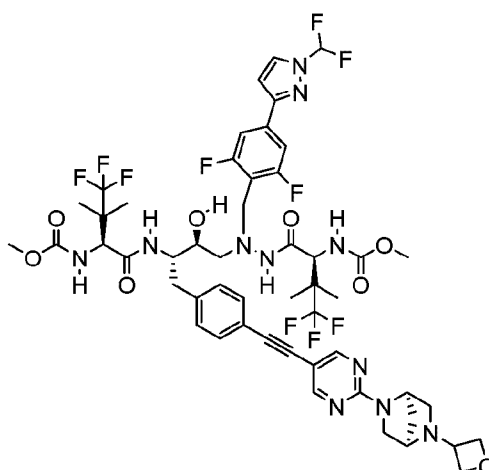
5



EXAMPLE 31

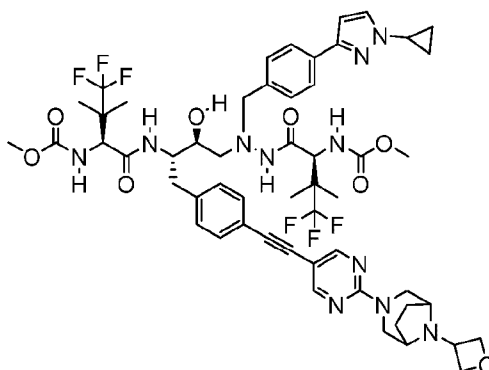
Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-(((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (31).

Intermediates: **I2**, **P13**, and **S29**. MS (ESI) m/z 1132.3 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.51 (s, 2H), 8.15 (d, J = 9.4 Hz, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.38 - 7.27 (m, 4H), 7.23 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 10.0 Hz, 1H), 6.77 (d, J = 9.8 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 5.18 (s, 1H), 4.93 (dt, J = 20.5, 7.3 Hz, 2H), 4.72 (s, 1H), 4.60 (td, J = 12.1, 11.2, 5.5 Hz, 1H), 4.51 (s, 1H), 4.46 - 4.39 (m, 1H), 4.36 - 4.24 (m, 1H), 4.18 - 4.07 (m, 2H), 3.93 (d, J = 11.4 Hz, 1H), 3.89 (s, 1H), 3.80 (d, J = 12.7 Hz, 1H), 3.76 - 3.67 (m, 5H), 3.66 (s, 2H), 2.96 - 2.70 (m, 4H), 2.33 (s, 2H), 1.22 - 1.04 (m, 12H), 1.02 (s, 3H).

**EXAMPLE 32**

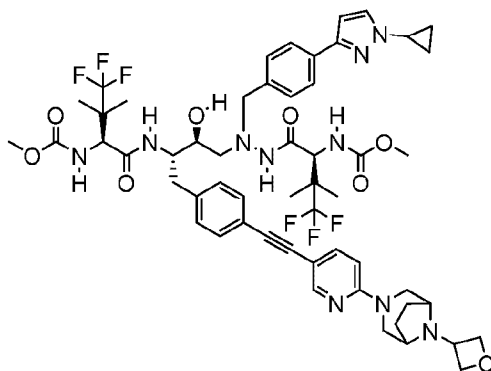
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((2-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (32).

Intermediates: **I2**, **P4**, and **S29**. MS (ESI) m/z 1142.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.51 (s, 2H), 8.14 (d, $J = 9.3$ Hz, 1H), 8.10 (d, $J = 2.7$ Hz, 1H), 7.52 (t, $J = 59.9$ Hz, 1H), 7.44 (d, $J = 8.2$ Hz, 2H), 7.34 (d, $J = 7.9$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 9.6$ Hz, 1H), 6.93 (d, $J = 2.7$ Hz, 1H), 6.78 (d, $J = 9.9$ Hz, 1H), 5.18 (s, 1H), 4.93 (dt, $J = 20.5, 7.3$ Hz, 2H), 4.71 (s, 1H), 4.60 (dq, $J = 11.6, 6.2, 5.6$ Hz, 2H), 4.51 (s, 1H), 4.44 (d, $J = 9.8$ Hz, 1H), 4.30 (d, $J = 9.9$ Hz, 1H), 4.21 - 4.05 (m, 2H), 3.94 (d, $J = 13.5$ Hz, 1H), 3.90 (d, $J = 12.9$ Hz, 1H), 3.80 (d, $J = 12.6$ Hz, 1H), 3.77 - 3.70 (m, 2H), 3.68 (s, 3H), 3.66 (s, 3H), 2.96 - 2.72 (m, 4H), 2.44 - 2.24 (m, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H).



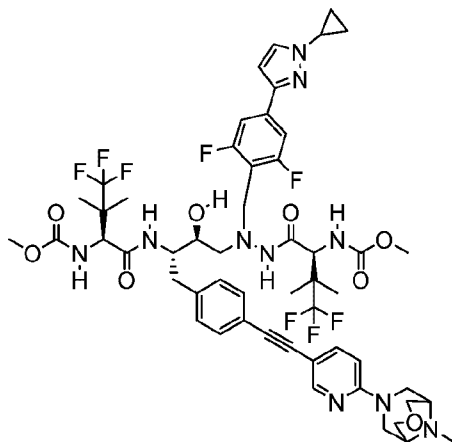
EXAMPLE 33

Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (33). Intermediates: **I2**, **P21**, and **S7**. MS (ESI) m/z 1142.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 2H), 8.10 (d, J = 9.5 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 2.3 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 9.5 Hz, 1H), 6.75 (d, J = 9.7 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.82 - 4.71 (m, 3H), 4.39 (d, J = 9.9 Hz, 1H), 4.24 (d, J = 9.7 Hz, 1H), 4.20 - 4.06 (m, 2H), 3.97 (d, J = 13.2 Hz, 1H), 3.87 (d, J = 13.4 Hz, 1H), 3.77 - 3.71 (m, 1H), 3.67 (s, 4H), 3.59 (s, 3H), 3.45 (d, J = 14.6 Hz, 2H), 2.93 - 2.86 (m, 2H), 2.85 - 2.67 (m, 1H), 2.31 - 2.15 (m, 2H), 2.06 - 1.93 (m, 2H), 1.15 - 1.03 (m, 10H), 1.01 (s, 3H), 0.82 (s, 3H).

**EXAMPLE 34**

Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (34). Intermediates: **I2**, **P21**, and **S3**. MS (ESI) m/z 1109.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.20 (d, J = 2.3 Hz, 1H), 8.03 (d, J = 9.5 Hz, 1H), 7.66 - 7.58 (m, 3H), 7.56 (d, J = 2.4 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 9.5 Hz, 1H), 6.76 (d, J = 8.9 Hz, 1H), 6.68 (d, J = 10.0 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 4.92 - 4.82 (m, 2H), 4.74 - 4.66 (m, 2H), 4.34 - 4.21 (m, 3H), 4.18 - 4.12 (m, 1H), 4.11 - 3.99 (m, 3H), 3.88 (d, J = 13.1 Hz, 1H), 3.78 (d, J = 13.3 Hz,

1H), 3.65 (d, J = 9.0 Hz, 1H), 3.60 - 3.53 (m, 4H), 3.51 (s, 3H), 3.28 (d, J = 13.8 Hz, 2H), 2.86 - 2.76 (m, 2H), 2.76 - 2.56 (m, 2H), 2.17 - 2.08 (m, 2H), 2.03 - 1.92 (m, 2H), 1.07 - 0.89 (m, 13H), 0.72 (s, 3H).

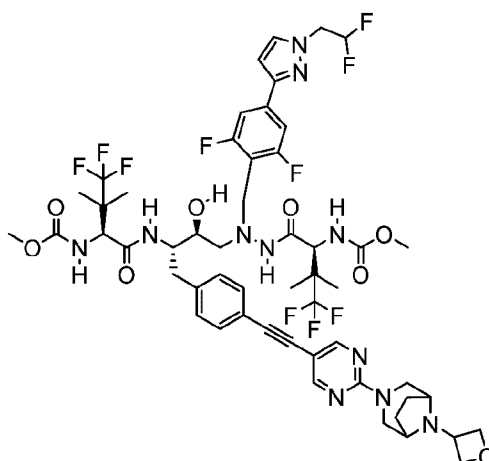


5

EXAMPLE 35

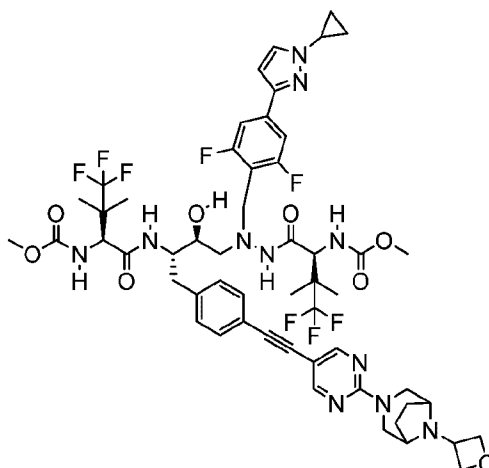
Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (35).

- 10 Intermediates: **I2**, **P13**, and **S2**. MS (ESI) m/z 1119.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.27 (dd, J = 2.3, 0.7 Hz, 1H), 8.16 (d, J = 9.4 Hz, 1H), 7.73 (dd, J = 9.0, 2.3 Hz, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.41 - 7.26 (m, 4H), 7.21 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 9.8 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 6.79 (d, J = 9.9 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 4.64 (d, J = 14.7 Hz, 2H), 4.53 - 4.41 (m, 1H), 4.35 - 4.25 (m, 1H), 4.22 - 4.06 (m, 7H), 3.93 (d, J = 13.2 Hz, 1H), 3.78 (dt, J = 14.9, 3.0 Hz, 2H), 3.73 - 3.67 (m, 4H), 3.66 (s, 3H), 3.63 (s, 2H), 3.19 (s, 3H), 2.94 - 2.72 (m, 4H), 1.21 - 0.99 (m, 16H).
- 15

**EXAMPLE 36**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (36).

Intermediates: **I2**, **P10**, and **S7**. MS (ESI) m/z 1170.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.53 (s, 2H), 8.19 (d, $J = 9.3$ Hz, 1H), 7.74 (d, $J = 2.4$ Hz, 1H), 7.37 (d, $J = 8.5$ Hz, 2H), 7.34 (d, $J = 8.1$ Hz, 2H), 7.23 (d, $J = 8.1$ Hz, 2H), 7.15 (d, $J = 10.0$ Hz, 1H), 6.81 (d, $J = 9.9$ Hz, 1H), 6.74 (d, $J = 2.4$ Hz, 1H), 6.22 (tt, $J = 55.3, 4.0$ Hz, 1H), 5.02 - 4.93 (m, 2H), 4.83 - 4.78 (m, 2H), 4.77 (s, 1H), 4.60 (td, $J = 14.3, 3.9$ Hz, 2H), 4.44 (d, $J = 10.0$ Hz, 1H), 4.31 (d, $J = 10.0$ Hz, 1H), 4.22 - 4.03 (m, 4H), 3.93 (d, $J = 13.2$ Hz, 1H), 3.72 (s, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 3.51 - 3.40 (m, 2H), 2.96 - 2.81 (m, 3H), 2.81 - 2.72 (m, 1H), 2.27 - 2.12 (m, 2H), 2.04 - 1.94 (m, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H).

**EXAMPLE 37**

Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-

16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((2-(8-(oxetan-3-yl)-3,8-

5 **diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-**
trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (37).

Intermediates: **I2**, **P13**, and **S7**. MS (ESI) m/z 1146.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol-

d₄) δ 8.43 (s, 2H), 8.10 (d, $J = 9.3$ Hz, 1H), 7.60 (d, $J = 2.4$ Hz, 1H), 7.25 (d, $J = 8.0$ Hz, 4H),

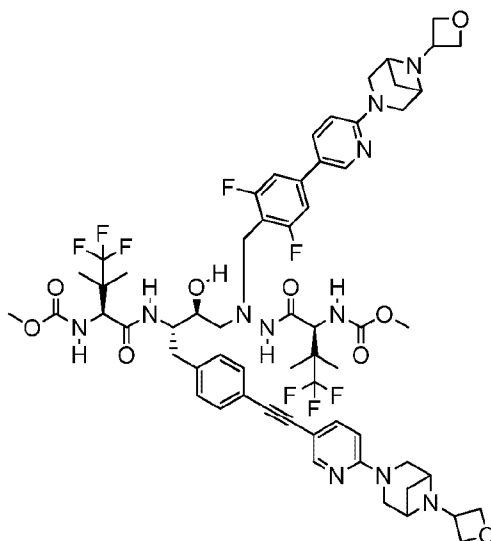
7.14 (d, $J = 8.1$ Hz, 2H), 7.07 (d, $J = 10.1$ Hz, 1H), 6.72 (d, $J = 10.0$ Hz, 1H), 6.55 (d, $J = 2.4$ Hz,

10 1H), 4.93 - 4.82 (m, 2H), 4.75 - 4.57 (m, 4H), 4.45 - 4.28 (m, 1H), 4.22 (d, $J = 10.0$ Hz, 1H),

4.14 - 3.97 (m, 4H), 3.83 (d, $J = 13.2$ Hz, 1H), 3.71 - 3.61 (m, 1H), 3.59 (s, 3H), 3.57 (s, 3H),

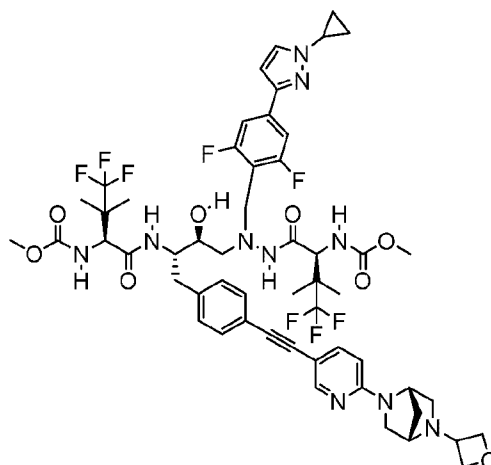
3.42 - 3.32 (m, 2H), 2.86 - 2.63 (m, 4H), 2.17 - 2.05 (m, 2H), 1.94 - 1.82 (m, 2H), 1.12 - 1.06

(m, 3H), 1.06 - 0.95 (m, 10H), 0.93 (s, 3H).

**EXAMPLE 38**

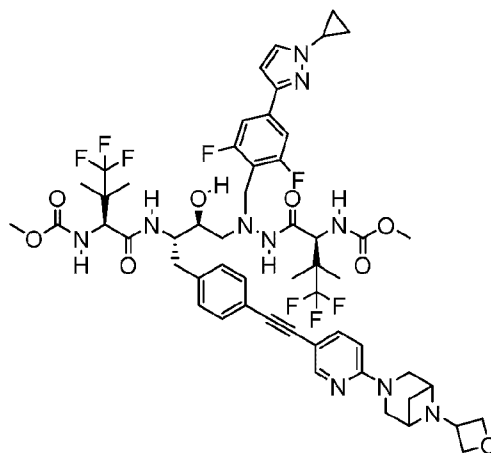
Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(6-(6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(((6-(6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (38). Intermediates: **I2**, **P22**, and **S4**. MS (ESI) m/z 1254.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.31 (d, $J = 2.4$ Hz, 1H), 8.15 (d, $J = 2.1$ Hz, 1H), 7.80 (d, $J = 9.0$ Hz, 1H), 7.62 - 7.51 (m, 1H), 7.23 (d, $J = 7.8$ Hz, 2H), 7.12 (d, $J = 8.0$ Hz, 2H), 7.08 (d, $J = 8.7$ Hz, 2H), 6.69 (d, $J = 9.0$ Hz, 1H), 6.60 (d, $J = 8.9$ Hz, 1H), 4.66 (t, $J = 6.5$ Hz, 4H), 4.40 - 4.31 (m, 6H), 4.04 (d, $J = 12.6$ Hz, 2H), 3.89 - 3.80 (m, 3H), 3.77 (t, $J = 6.3$ Hz, 4H), 3.61 (d, $J = 1.2$ Hz, 3H), 3.57 (s, 3H), 3.48 (d, $J = 13.4$ Hz, 8H), 2.89 - 2.55 (m, 6H), 1.57 (t, $J = 8.8$ Hz, 2H), 1.24 - 1.13 (m, 3H), 1.08 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H), 0.95 (s, 3H).

15

**EXAMPLE 39**

Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(((6-((1S,4S)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (39).

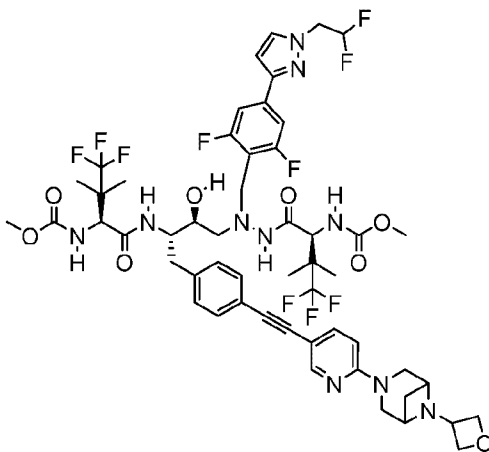
Intermediates: **I2**, **P13**, and **S30**. MS (ESI) m/z 1131.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.16 (d, $J = 2.2$ Hz, 1H), 8.10 (d, $J = 9.2$ Hz, 1H), 7.61 (d, $J = 2.4$ Hz, 2H), 7.59 (d, $J = 2.2$ Hz, 1H), 7.29 - 7.19 (m, 5H), 7.12 (d, $J = 8.0$ Hz, 2H), 6.73 (d, $J = 10.0$ Hz, 1H), 6.63 - 6.52 (m, 2H), 4.95 (s, 1H), 4.89 - 4.83 (m, 1H), 4.65 - 4.56 (m, 1H), 4.54 - 4.43 (m, 2H), 4.41 (s, 1H), 4.35 (d, $J = 9.9$ Hz, 1H), 4.22 (d, $J = 9.9$ Hz, 1H), 4.12 - 3.97 (m, 2H), 3.83 (d, $J = 13.2$ Hz, 1H), 3.70 (d, $J = 11.8$ Hz, 1H), 3.65 - 3.61 (m, 1H), 3.59 (s, 3H), 3.57 (s, 3H), 2.86 - 2.60 (m, 4H), 2.23 (s, 2H), 1.10 - 0.95 (m, 13H), 0.93 (s, 3H).



EXAMPLE 40

Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(((6-(6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (40).

Intermediates: **I2**, **P13**, and **S4**. MS (ESI) m/z 1131.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.23 (d, J = 2.3 Hz, 1H), 8.09 (d, J = 9.5 Hz, 1H), 7.64 (dd, J = 8.8, 2.3 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 7.23 (dd, J = 8.4, 3.3 Hz, 4H), 7.12 (d, J = 8.1 Hz, 2H), 6.68 (d, J = 8.9 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 4.93 - 4.83 (m, 2H), 4.51 (dd, J = 8.2, 4.0 Hz, 2H), 4.34 (s, 1H), 4.27 - 4.18 (m, 1H), 4.12 - 3.94 (m, 4H), 3.83 (d, J = 13.2 Hz, 1H), 3.65 - 3.60 (m, 1H), 3.59 (s, 3H), 3.56 (s, 3H), 2.85 - 2.62 (m, 4H), 2.01 (d, J = 11.0 Hz, 1H), 1.18 (d, J = 13.9 Hz, 1H), 1.10 - 0.94 (m, 13H), 0.92 (s, 3H).



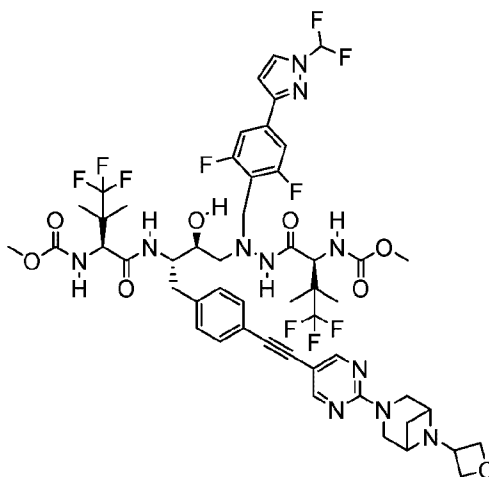
15

EXAMPLE 41

Methyl ((5S,8S,9S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(((6-(6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (41).

Intermediates: **I2**, **P10**, and **S4**. MS (ESI) m/z 1155.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.24 (d, J = 2.2 Hz, 1H), 8.10 (d, J = 9.3 Hz, 1H), 7.69 - 7.60 (m, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 6.69 (d, J = 9.0 Hz, 1H), 6.65 (d, J = 2.5 Hz, 1H), 6.13 (tt, J = 55.3, 3.9 Hz, 1H), 4.58 - 4.42 (m, 4H), 4.35 (s, 1H), 4.27 - 4.18 (m, 1H), 4.16 - 3.95 (m, 4H), 3.84 (d, J = 13.3 Hz, 1H), 3.63 (s, 2H), 3.60 (s, 3H), 3.57 (s, 3H), 2.86 -

2.72 (m, 3H), 2.72 - 2.58 (m, 1H), 2.02 (d, J = 11.0 Hz, 1H), 1.19 (d, J = 13.9 Hz, 1H), 1.07 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H).



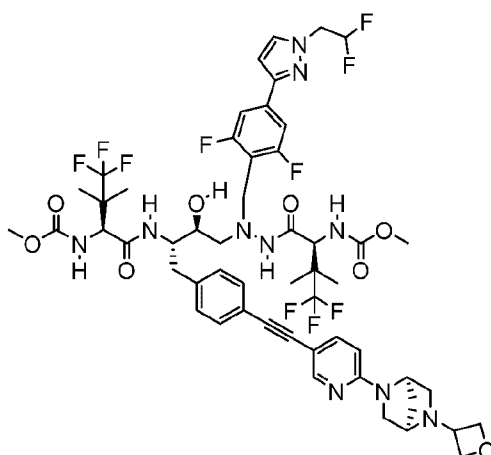
EXAMPLE 42

5 **Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-(6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trifluoro-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (42).**

Intermediates: **I2**, **P4**, and **S52**. MS (ESI) m/z 1143.8 [M+H]⁺. ¹H NMR (400 MHz, Methanol-

10 d4) δ 8.57 (s, 2H), 8.19 (d, J = 9.4 Hz, 0H), 8.11 (d, J = 2.8 Hz, 1H), 7.70 - 7.51 (m, 4H), 7.44 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 7.9 Hz, 2H), 7.28 - 7.20 (m, 2H), 6.93 (d, J = 2.8 Hz, 1H), 4.65 (d, J = 7.4 Hz, 2H), 4.49 - 4.41 (m, 2H), 4.37 - 4.28 (m, 2H), 4.27 - 4.11 (m, 4H), 3.91 (dd, J = 25.4, 13.9 Hz, 2H), 3.73 (s, 2H), 3.70 (s, 3H), 3.67 (s, 3H), 2.94 - 2.83 (m, 3H), 2.83 - 2.70 (m, 1H), 2.09 (t, J = 11.9 Hz, 1H), 1.18 - 1.13 (m, 6H), 1.12 (s, 3H), 1.02 (s, 3H).

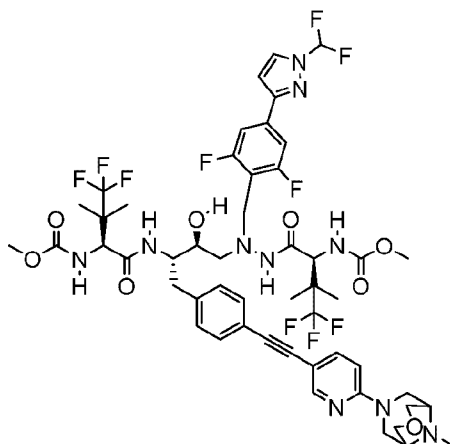
15



EXAMPLE 43

Methyl ((5S,8S,9S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (43).

Intermediates: **I2**, **P10**, and **S6**. MS (ESI) m/z 1155.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.25 (d, $J = 1.9$ Hz, 1H), 8.19 (d, $J = 9.4$ Hz, 1H), 7.74 (d, $J = 2.5$ Hz, 1H), 7.69 (dd, $J = 8.6, 2.3$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 2H), 7.32 (d, $J = 7.8$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 6.82 (d, $J = 9.9$ Hz, 1H), 6.75 (d, $J = 2.4$ Hz, 1H), 6.66 (d, $J = 8.8$ Hz, 1H), 6.39 - 6.05 (m, 1H), 5.06 - 5.02 (m, 1H), 4.74 - 4.67 (m, 1H), 4.65 - 4.53 (m, 2H), 4.50 (s, 1H), 4.44 (d, $J = 9.9$ Hz, 1H), 4.31 (d, $J = 10.0$ Hz, 1H), 4.13 (d, $J = 13.4$ Hz, 2H), 3.93 (d, $J = 13.3$ Hz, 1H), 3.83 - 3.72 (m, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 2.94 - 2.72 (m, 2H), 2.33 (s, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H).

**EXAMPLE 44**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-

16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(9-methyl-3-oxa-7,9-

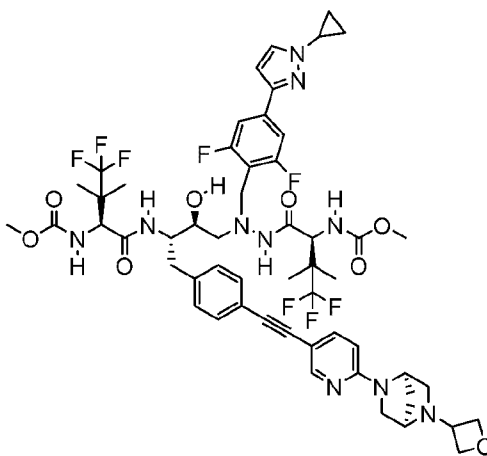
5 diazabicyclo[3.3.1]nonan-7-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (44).

Intermediates: **I2**, **P4**, and **S2**. MS (ESI) m/z 1130.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol-

d_4) δ 8.18 (d, $J = 2.3$ Hz, 1H), 8.10 (d, $J = 9.3$ Hz, 1H), 8.01 (d, $J = 2.7$ Hz, 1H), 7.58 (dd, $J = 9.2, 2.6$ Hz, 1H), 7.44 (t, $J = 59.7$ Hz, 1H), 7.36 (d, $J = 8.2$ Hz, 2H), 7.23 (d, $J = 7.8$ Hz, 2H),

7.12 (d, $J = 8.0$ Hz, 2H), 7.09 - 7.00 (m, 1H), 6.85 (d, $J = 2.8$ Hz, 1H), 6.78 (d, $J = 8.9$ Hz, 1H), 6.72 (d, $J = 10.0$ Hz, 1H), 4.35 (d, $J = 9.9$ Hz, 1H), 4.21 (d, $J = 9.9$ Hz, 1H), 4.13 - 3.94 (m, 5H), 3.85 (d, $J = 13.2$ Hz, 1H), 3.71 - 3.63 (m, 3H), 3.60 (s, 3H), 3.57 (s, 3H), 3.51 (s, 2H), 3.10 (s, 3H), 2.88 - 2.73 (m, 3H), 2.73 - 2.64 (m, 1H), 1.07 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H).

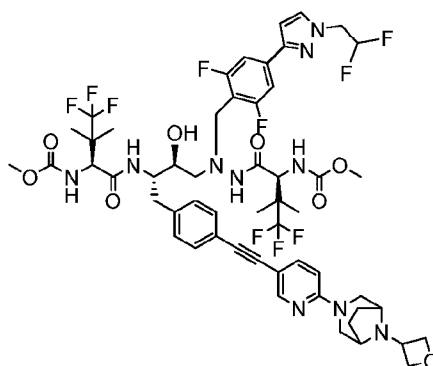
15



EXAMPLE 45

Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (45).

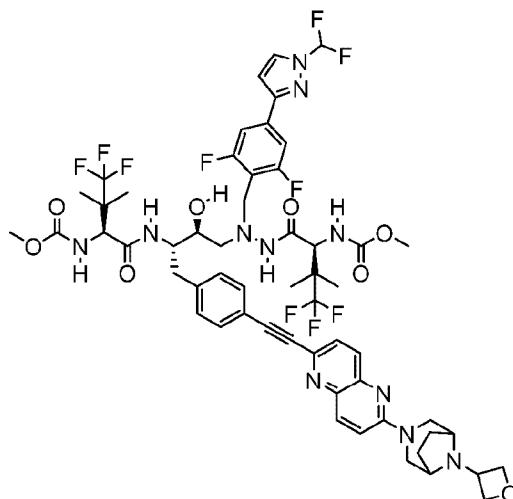
Intermediates: **I2**, **P13**, and **S6**. MS (ESI) m/z 1130.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.16 (d, J = 2.2 Hz, 1H), 8.10 (d, J = 9.3 Hz, 1H), 7.65 - 7.55 (m, 2H), 7.30 - 7.19 (m, 4H), 7.12 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 10.0 Hz, 1H), 6.72 (d, J = 9.9 Hz, 1H), 6.58 (d, J = 8.8 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 4.96 (s, 1H), 4.86 (dd, J = 8.3, 6.4 Hz, 1H), 4.61 (dd, J = 8.5, 4.6 Hz, 1H), 4.56 - 4.44 (m, 2H), 4.42 (s, 1H), 4.35 (d, J = 9.8 Hz, 1H), 4.22 (d, J = 10.0 Hz, 1H), 4.08 - 3.98 (m, 2H), 3.83 (d, J = 13.2 Hz, 1H), 3.73 - 3.61 (m, 4H), 3.59 (s, 3H), 3.57 (s, 3H), 2.85 - 2.72 (m, 2H), 2.72 - 2.62 (m, 1H), 2.24 (s, 2H), 1.07 (s, 3H), 1.06 - 0.94 (m, 10H), 0.93 (s, 3H).

**EXAMPLE 46**

Methyl ((5S,10S,11S,14S)-8-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-10-hydroxy-15,15-dimethyl-11-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,8,12-tetraazahexadecan-14-yl)carbamate (46).

Intermediates: **I2**, **P10**, and **S3**. MS (ESI) m/z 1169.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.30 (d, J = 2.3 Hz, 1H), 8.19 (d, J = 9.3 Hz, 1H), 7.74 (d, J = 2.4 Hz, 1H), 7.70 (dd, J = 8.9, 2.3 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.19 - 7.12 (m, 1H), 6.86 (d, J = 8.9 Hz, 1H), 6.81 (d, J = 9.9 Hz, 1H), 6.74 (d, J = 2.5 Hz, 1H), 6.22 (tt, J = 55.5, 4.2 Hz, 1H), 4.97 (t, J = 7.6 Hz, 3H), 4.80 (dd, J = 8.2, 5.0 Hz, 2H), 4.60 (td, J = 14.2, 3.9 Hz, 2H), 4.44 (d, J = 9.9 Hz, 1H), 4.36 (d, J = 13.6 Hz, 2H), 4.31 (d, J = 10.0 Hz, 1H),

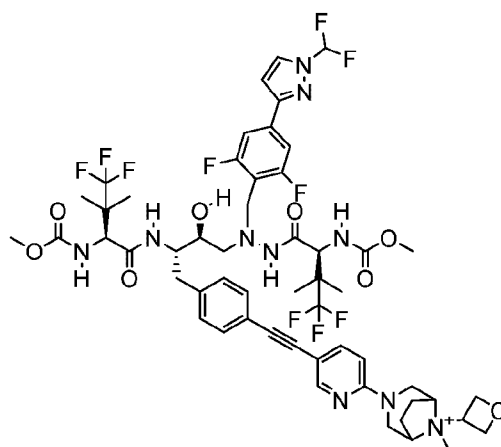
4.19 - 4.10 (m, 4H), 3.93 (d, J = 13.2 Hz, 1H), 3.77 - 3.71 (m, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 3.37 (d, J = 13.8 Hz, 2H), 2.96 - 2.69 (m, 4H), 2.29 - 2.16 (m, 2H), 2.16 - 2.03 (m, 2H), 1.17 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H).



EXAMPLE 47

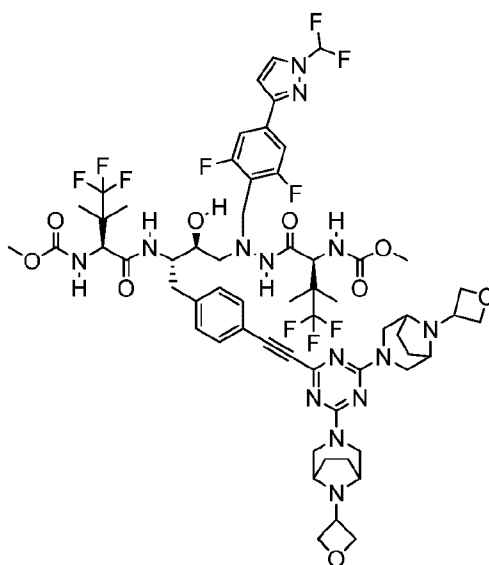
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-1,5-naphthyridin-2-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (47).

Intermediates: **I2**, **P4**, and **S31**. MS (ESI) m/z 1206.3 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.23 (d, J = 9.4 Hz, 1H), 8.16 - 8.10 (m, 2H), 8.09 (d, J = 8.7 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.54 (t, J = 59.5 Hz, 1H), 7.52 (d, J = 9.6 Hz, 1H), 7.50 - 7.43 (m, 4H), 7.30 (d, J = 8.0 Hz, 2H), 7.22 - 7.13 (m, 1H), 6.95 (d, J = 2.8 Hz, 1H), 6.85 (d, J = 10.0 Hz, 1H), 4.99 (t, J = 7.6 Hz, 2H), 4.84 (dd, J = 8.3, 5.0 Hz, 2H), 4.65 (d, J = 14.1 Hz, 2H), 4.45 (d, J = 9.9 Hz, 1H), 4.31 (d, J = 9.9 Hz, 1H), 4.27 - 4.11 (m, 4H), 3.95 (d, J = 13.2 Hz, 1H), 3.84 - 3.74 (m, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 2.99 - 2.83 (m, 3H), 2.83 - 2.74 (m, 1H), 2.30 - 2.19 (m, 2H), 2.17 - 2.06 (m, 2H), 1.17 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.04 (s, 3H).

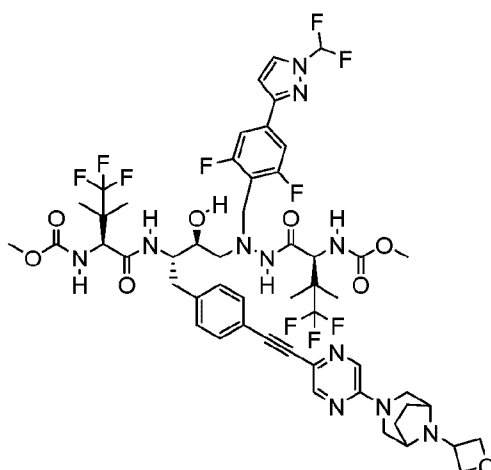
**EXAMPLE 48**

3-(5-((4-((2S,3S)-4-(1-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-2-((S)-4,4,4-trifluoro-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)hydrazinyl)-3-hydroxy-2-((S)-4,4,4-trifluoro-2-((methoxycarbonyl)amino)-3,3-dimethylbutanamido)butyl)phenyl)ethynyl)pyridin-2-yl)-8-methyl-8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-8-ium (48).

Intermediates: **I2**, **P4**, and **S54** and **S55**. MS (ESI) m/z 1169.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.21 (d, $J = 2.5$ Hz, 1H), 8.10 (d, $J = 9.4$ Hz, 1H), 8.01 (d, $J = 2.7$ Hz, 1H), 7.64 - 7.57 (m, 1H), 7.44 (t, $J = 60.3$ Hz, 1H), 7.36 (d, $J = 8.2$ Hz, 2H), 7.23 (d, $J = 7.9$ Hz, 2H), 7.13 (d, $J = 8.0$ Hz, 2H), 7.07 (d, $J = 9.8$ Hz, 1H), 6.85 (d, $J = 2.8$ Hz, 1H), 6.73 (d, $J = 10.6$ Hz, 1H), 6.70 (d, $J = 9.0$ Hz, 1H), 5.55 - 5.45 (m, 1H), 5.00 - 4.83 (m, 4H), 4.35 (d, $J = 9.9$ Hz, 1H), 4.21 (d, $J = 10.0$ Hz, 1H), 4.14 (s, 2H), 4.12 - 3.94 (m, 4H), 3.85 (d, $J = 13.2$ Hz, 1H), 3.71 - 3.62 (m, 2H), 3.59 (d, $J = 1.2$ Hz, 3H), 3.57 (d, $J = 1.5$ Hz, 3H), 3.50 (d, $J = 2.0$ Hz, 1H), 3.46 (s, 3H), 2.88 - 2.73 (m, 3H), 2.73 - 2.63 (m, 1H), 2.49 - 2.38 (m, 1.5H), 2.28 (d, $J = 11.3$ Hz, 0.5H), 2.20 - 2.05 (m, 2H), 1.06 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H).



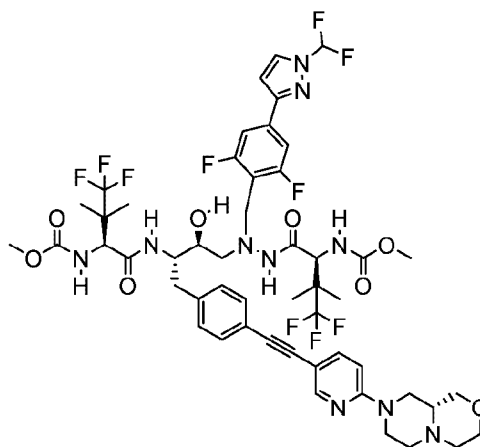
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((4-((1R,5S)-8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-1,3,5-triazin-2-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (49). Intermediates: **I2**, **P4**, and **S32**. MS (ESI) m/z 1323.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.20 (d, J = 9.4 Hz, 1H), 8.11 (d, J = 2.7 Hz, 1H), 7.53 (t, J = 59.6 Hz, 1H), 7.50 - 7.40 (m, 4H), 7.20 - 7.11 (m, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.75 (d, J = 9.7 Hz, 1H), 5.00 - 4.91 (m, 4H), 4.83 - 4.68 (m, 4H), 4.54 - 4.39 (m, 3H), 4.33 - 4.27 (m, 1H), 4.21 - 4.04 (m, 6H), 3.94 (d, J = 13.1 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 3.51 - 3.39 (m, 5H), 3.00 - 2.72 (m, 4H), 2.37 - 2.11 (m, 4H), 2.03 - 1.84 (m, 4H), 1.16 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 1.03 (s, 3H).

**EXAMPLE 50**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((5-(8-(oxetan-3-yl)-3,8-

5 diazabicyclo[3.2.1]octan-3-yl)pyrazin-2-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (50).

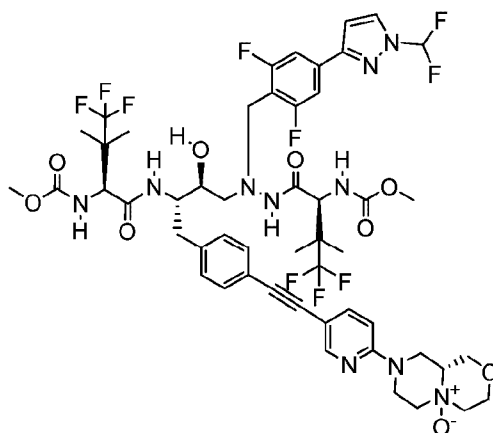
Intermediates: **I2**, **P4**, and **S33**. MS (ESI) m/z 1156.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol-
 d4) δ 8.34 (d, $J = 1.3$ Hz, 1H), 8.25 (s, 1H), 8.16 (d, $J = 9.3$ Hz, 1H), 8.10 (d, $J = 2.7$ Hz, 1H),
 7.53 (t, $J = 59.4$ Hz, 1H), 7.45 (d, $J = 8.3$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz,
 10 2H), 6.93 (d, $J = 2.8$ Hz, 1H), 4.97 (t, $J = 7.6$ Hz, 2H), 4.82 - 4.76 (m, 2H), 4.47 - 4.36 (m, 3H),
 4.30 (d, $J = 9.9$ Hz, 1H), 4.23 - 4.10 (m, 4H), 3.95 (d, $J = 12.9$ Hz, 1H), 3.78 - 3.72 (m, 1H), 3.69
 (s, 3H), 3.66 (s, 3H), 3.46 (d, $J = 14.0$ Hz, 3H), 2.96 - 2.71 (m, 4H), 2.27 - 2.20 (m, 1H), 2.14 -
 2.02 (m, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H).



EXAMPLE 51

methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-8-(4-((6-((R)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)pyridin-3-yl)ethynyl)benzyl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (51).

Intermediates: **I2**, **P4**, and **S8**. MS (ESI) m/z 1129.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.24 - 8.15 (m, 1H), 8.08 (d, J = 9.4 Hz, 1H), 8.01 (d, J = 2.7 Hz, 1H), 7.61 (dd, J = 8.8, 2.3 Hz, 1H), 7.44 (t, J = 59.7 Hz, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 6.89 - 6.79 (m, 2H), 4.60 - 4.44 (m, 1H), 4.34 (s, 1H), 4.25 - 4.18 (m, 1H), 4.11 - 3.98 (m, 4H), 3.85 (d, J = 13.2 Hz, 1H), 3.76 (t, J = 12.6 Hz, 1H), 3.68 - 3.62 (m, 1H), 3.60 (s, 3H), 3.57 (s, 3H), 3.54 - 3.35 (m, 2H), 2.85 - 2.74 (m, 4H), 2.73 - 2.64 (m, 1H), 1.07 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H).



15

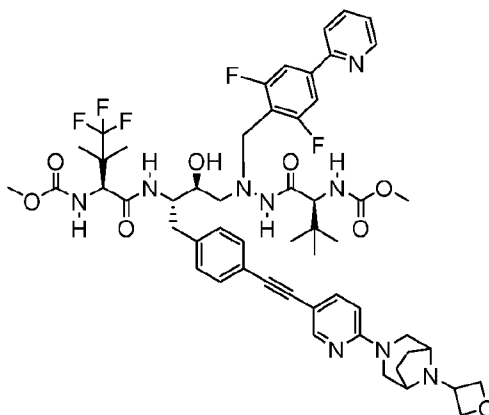
EXAMPLE 52

(9aR)-8-(5-((4-((2S,3S)-4-(1-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-2-((S)-4,4,4-trifluoro-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)hydrazinyl)-3-hydroxy-2-((S)-4,4,4-trifluoro-2-((methoxycarbonyl)amino)-3,3-dimethylbutanamido)butyl)phenyl) ethynyl)pyridin-2-yl)octahydro-5H-pyrazino[2,1-

c][1,4]oxazine 5-oxide (52). To a solution of **51** (17 mg, 0.02 mmol) in CH_3CN (1 mL) was added 3-Chloroperoxybenzoic acid (77%, 3.9 mg, 0.02 mmol) the mixture was stirred for 5 min then purified by HPLC to afford **52**. MS (ESI) m/z 1146.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.38 - 8.23 (m, 1H), 8.17 - 8.06 (m, 2H), 7.99 - 7.88 (m, 0H), 7.73 - 7.65 (m, 1H), 7.59 - 7.40 (m, 3H), 7.33 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 10.2 Hz,

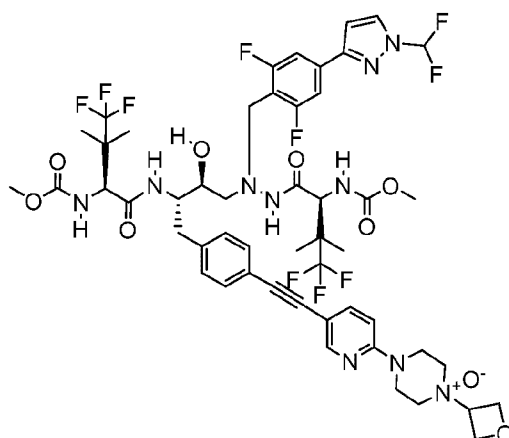
1H), 6.98 - 6.91 (m, 2H), 6.77 (d, J = 10.1 Hz, 1H), 4.59 (d, J = 14.5 Hz, 1H), 4.41 (dd, J = 21.3, 12.0 Hz, 2H), 4.28 (dd, J = 17.0, 11.1 Hz, 2H), 4.14 (d, J = 12.9 Hz, 2H), 4.10 - 3.87 (m, 6H), 3.67 (d, J = 10.5 Hz, 8H), 3.26 - 3.12 (m, 1H), 3.00 - 2.73 (m, 4H), 2.02 (s, 2H), 1.24 - 1.10 (m, 10H), 1.02 (s, 3H).

5



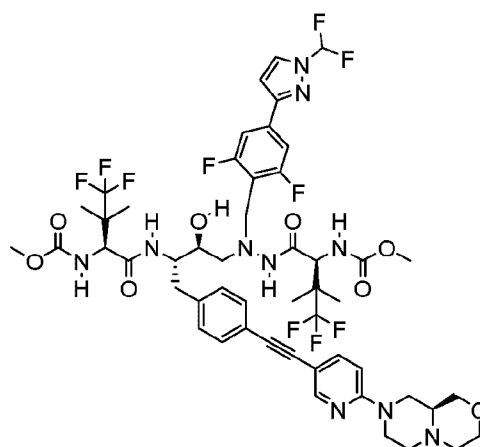
EXAMPLE 53

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyridin-2-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (53). Intermediates: **I3**, **P28**, and **S3**. MS (ESI) m/z 1062.4 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.64 (d, J = 4.9 Hz, 1H), 8.30 (d, J = 2.2 Hz, 1H), 8.15 (d, J = 9.3 Hz, 1H), 7.91 (s, 2H), 7.70 (dd, J = 8.7, 2.3 Hz, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.9 Hz, 1H), 6.77 (d, J = 10.5 Hz, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.82 - 4.76 (m, 4H), 4.40 (dd, J = 33.8, 12.0 Hz, 3H), 4.16 (d, J = 12.1 Hz, 4H), 4.00 (d, J = 13.3 Hz, 1H), 3.79 - 3.60 (m, 9H), 3.37 (d, J = 14.0 Hz, 3H), 2.95 - 2.77 (m, 4H), 2.22 (s, 2H), 2.08 (d, J = 8.7 Hz, 2H), 1.13 (d, J = 11.3 Hz, 6H), 0.86 (s, 10H).



EXAMPLE 54

4-(5-((4-((2S,3S)-4-(1-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-2-((S)-4,4,4-trifluoro-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)hydrazinyl)-3-hydroxy-2-((S)-4,4,4-trifluoro-2-((methoxycarbonyl)amino)-3,3-dimethylbutanamido)butyl)phenyl)ethynyl)pyridin-2-yl)-1-(oxetan-3-yl)piperazine 1-oxide (**54**). The title compound **54** was prepared according to the method presented for the synthesis of compound **52** but instead utilizing **112**. MS (ESI) m/z 1145.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.31 (d, J = 2.2 Hz, 1H), 8.19 - 8.05 (m, 2H), 7.77 - 7.59 (m, 2H), 7.59 - 7.51 (m, 1H), 7.44 (d, J = 8.2 Hz, 2H), 7.39 - 7.30 (m, 3H), 7.22 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 10.0 Hz, 1H), 7.01 - 6.88 (m, 2H), 6.77 (d, J = 9.9 Hz, 1H), 5.14 - 5.00 (m, 3H), 4.94 (dd, J = 8.1, 6.7 Hz, 2H), 4.47 (dd, J = 25.9, 10.4 Hz, 3H), 4.37 - 4.24 (m, 1H), 4.14 (d, J = 13.0 Hz, 2H), 3.95 (d, J = 13.2 Hz, 1H), 3.87 - 3.57 (m, 14H), 2.98 - 2.67 (m, 4H), 1.25 - 1.06 (m, 10H), 1.02 (s, 3H).

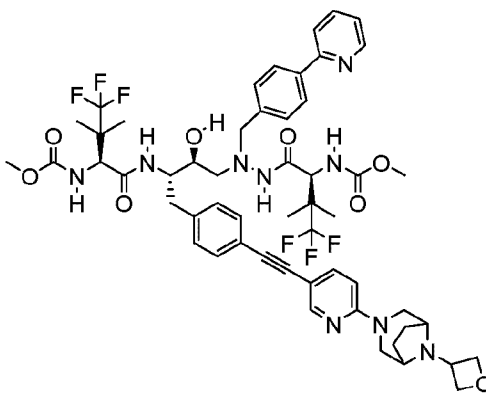


EXAMPLE 55

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-

16,16,16-trifluoro-8-(4-(((S)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)pyridin-3-yl)ethynyl)benzyl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (55).

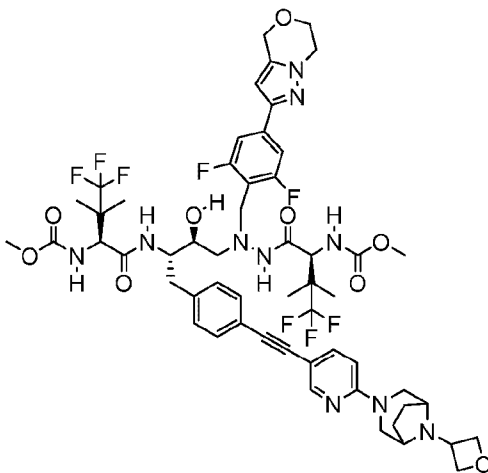
Intermediates: **I2**, **P4**, and **S9**. MS (ESI) m/z 1129.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.21 (dd, $J = 2.2, 0.8$ Hz, 1H), 8.01 (d, $J = 2.7$ Hz, 1H), 7.61 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.44 (t, $J = 59.6$ Hz, 1H), 7.36 (d, $J = 8.3$ Hz, 2H), 7.24 (d, $J = 7.9$ Hz, 2H), 7.13 (d, $J = 8.1$ Hz, 2H), 6.90 - 6.83 (m, 2H), 4.60 - 4.44 (m, 1H), 4.34 (s, 1H), 4.21 (s, 1H), 4.14 - 3.98 (m, 4H), 3.85 (d, $J = 13.1$ Hz, 1H), 3.76 (t, $J = 12.6$ Hz, 1H), 3.67 - 3.62 (m, 1H), 3.60 (s, 3H), 3.57 (s, 3H), 3.54 - 3.35 (m, 2H), 2.88 - 2.73 (m, 4H), 2.73 - 2.66 (m, 1H), 1.07 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H).



EXAMPLE 56

Methyl ((5S,8S,9S,14S)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-11-(4-(pyridin-2-yl)benzyl)-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-

5 tetraazahexadecan-14-yl)carbamate (56). Intermediates: **I2**, **P30**, and **S3**. MS (ESI) m/z 1081.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.75 (d, J = 5.6 Hz, 1H), 8.41 (t, J = 8.0 Hz, 1H), 8.36 - 8.25 (m, 1H), 8.20 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 9.5 Hz, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.81 (t, J = 6.6 Hz, 1H), 7.74 - 7.63 (m, 3H), 7.33 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 9.9 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 6.81 (d, J = 9.8 Hz, 1H), 4.96 (dd, J = 8.1, 7.1 Hz, 2H), 4.81 (dd, J = 8.2, 5.0 Hz, 2H), 4.44 - 4.30 (m, 3H), 4.24 (d, J = 9.6 Hz, 1H), 4.16 (s, 2H), 4.08 (d, J = 13.6 Hz, 1H), 3.99 (d, J = 13.4 Hz, 1H), 3.76 (s, 1H), 3.68 (s, 3H), 3.56 (s, 3H), 3.38 (d, J = 13.7 Hz, 2H), 2.98 - 2.72 (m, 3H), 2.27 - 2.16 (m, 2H), 2.12 - 2.03 (m, 2H), 1.12 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H), 0.84 (s, 3H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.36, -77.68, -77.89.



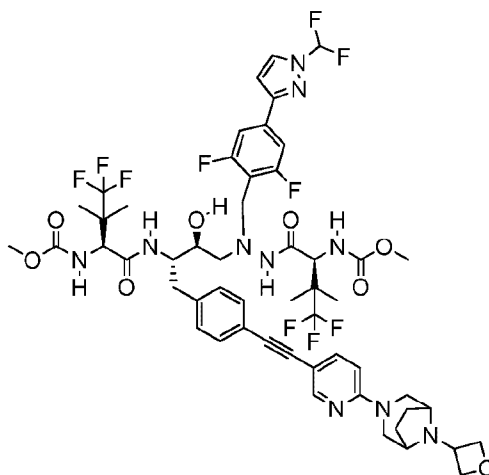
15

EXAMPLE 57

Methyl ((5S,8S,9S,14S)-11-(4-(6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (57).

Intermediates: **I2**, **P27**, and **S3**. MS (ESI) m/z 1161.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.29 (d, J = 2.3 Hz, 1H), 8.18 (d, J = 9.3 Hz, 1H), 7.70 (dd, J = 8.9, 2.3 Hz, 1H), 7.42 -

7.31 (m, 4H), 7.22 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 9.9 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 6.81 (d, J = 9.9 Hz, 1H), 6.48 (s, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.85 (s, 2H), 4.81 (dd, J = 8.3, 5.0 Hz, 2H), 4.47 - 4.39 (m, 1H), 4.35 (d, J = 14.5 Hz, 2H), 4.33 - 4.26 (m, 1H), 4.22 - 4.07 (m, 9H), 3.93 (d, J = 13.3 Hz, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 3.44 - 3.35 (m, 2H), 2.96 - 2.71 (m, 4H), 2.27 - 2.17 (m, 2H), 2.08 (d, J = 8.6 Hz, 2H), 1.17 (s, 3H), 1.15 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H). ¹⁹F NMR (377 MHz, Methanol-d₄) δ -77.40, -77.74, -77.92, -115.37.



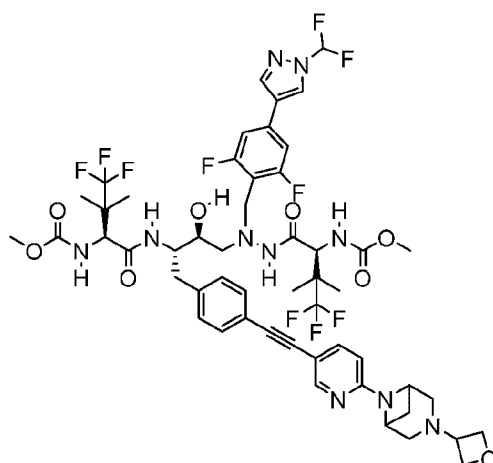
10

EXAMPLE 58

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (58) (GS-PI1).

15 Intermediates: **I2**, **P4**, and **S3**. MS (ESI) m/z 1155.6 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.29 (dd, J = 2.3, 0.7 Hz, 1H), 8.18 (d, J = 9.3 Hz, 1H), 8.11 (d, J = 2.7 Hz, 1H), 7.72 - 7.68 (m, 1H), 7.54 (d, J = 59.9 Hz, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 10.0 Hz, 1H), 6.94 (d, J = 2.7 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 6.81 (d, J = 9.9 Hz, 1H), 4.99 - 4.92 (m, 2H), 4.84 - 4.77 (m, 2H), 4.44 (d, J = 9.9 Hz, 1H), 4.40 - 4.26 (m, 3H), 4.22 - 4.09 (m, 4H), 3.94 (d, J = 13.2 Hz, 1H), 3.78 - 3.70 (m, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 3.38 (d, J = 13.9 Hz, 2H), 2.95 - 2.70 (m, 4H), 2.30 - 2.15 (m, 2H), 2.15 - 2.03 (m, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H). ¹⁹F NMR (377 MHz, Methanol-d₄) δ -77.40, -77.73, -77.90, -96.95 (dd, J = 59.9, 19.6 Hz), -114.92.

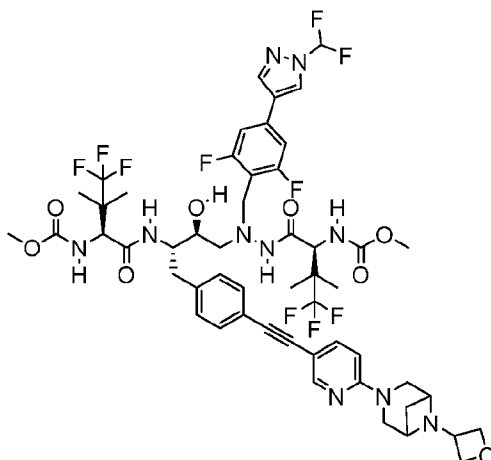
20

**EXAMPLE 59**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-

16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(3-(oxetan-3-yl)-3,6-
diazabicyclo[3.1.1]heptan-6-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-
2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (59).

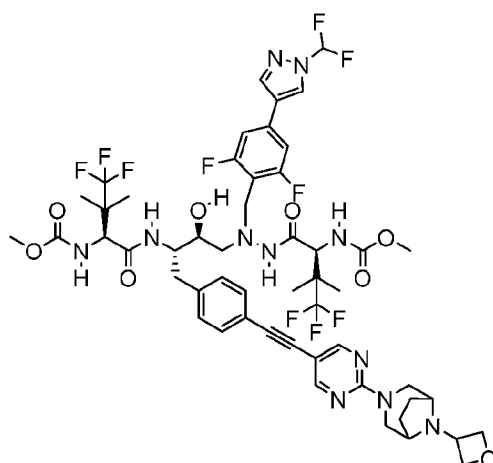
Intermediates: **I2**, **P7**, and **S34**. MS (ESI) m/z 1141.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol-
 d4) δ 8.54 (d, J = 0.8 Hz, 1H), 8.37 - 8.24 (m, 1H), 8.18 (d, J = 9.3 Hz, 1H), 8.13 (s, 1H), 7.79
 10 (dd, J = 8.6, 2.2 Hz, 1H), 7.51 (t, J = 59.7 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.29 - 7.20 (m, 4H),
 7.18 (d, J = 9.8 Hz, 1H), 6.82 (d, J = 9.8 Hz, 1H), 6.73 (d, J = 8.7 Hz, 1H), 4.77 (t, J = 7.6 Hz,
 2H), 4.62 (d, J = 6.3 Hz, 2H), 4.53 (dd, J = 8.3, 5.1 Hz, 2H), 4.49 - 4.41 (m, 1H), 4.37 - 4.29 (m,
 1H), 4.27 - 4.07 (m, 3H), 3.93 (d, J = 13.2 Hz, 1H), 3.69 (s, 3H), 3.68 - 3.61 (m, 4H), 3.00 (dt, J
 = 10.2, 6.3 Hz, 1H), 2.94 - 2.72 (m, 4H), 2.09 - 1.98 (m, 1H), 1.17 (s, 3H), 1.15 (s, 3H), 1.12 (s,
 15 3H), 1.03 (s, 3H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.39, -77.71, -77.96, -96.87 (d, J =
 59.7 Hz), -115.01.

**EXAMPLE 60**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-

16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(6-(oxetan-3-yl)-3,6-
diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-
2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (60).

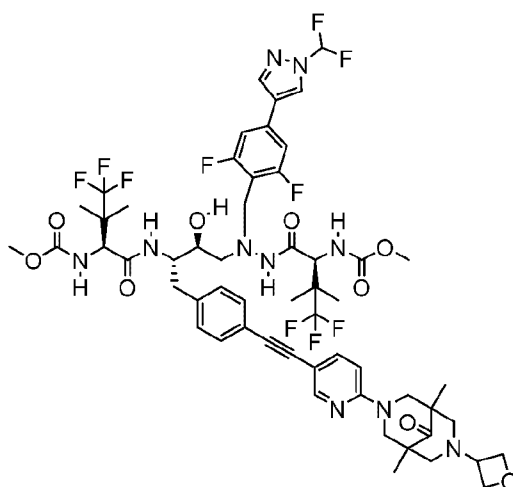
Intermediates: **I2**, **P7**, and **S4**. MS (ESI) m/z 1141.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol-
 d4) δ 8.54 (d, $J = 0.7$ Hz, 1H), 8.37 - 8.29 (m, 1H), 8.17 (d, $J = 9.4$ Hz, 1H), 8.13 (s, 1H), 7.74
 10 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.51 (t, $J = 59.7$ Hz, 1H), 7.34 (d, $J = 7.9$ Hz, 2H), 7.24 (dd, $J = 12.7,$
 8.2 Hz, 4H), 7.18 (d, $J = 10.1$ Hz, 1H), 6.84 - 6.76 (m, 2H), 5.08 - 4.93 (m, 2H), 4.65 - 4.56 (m,
 2H), 4.50 - 4.41 (m, 1H), 4.39 - 4.27 (m, 1H), 4.21 - 4.03 (m, 3H), 3.93 (d, $J = 13.2$ Hz, 1H),
 3.78 - 3.68 (m, 4H), 3.67 (s, 3H), 2.95 - 2.73 (m, 4H), 2.11 (d, $J = 11.1$ Hz, 1H), 1.17 (s, 3H),
 1.15 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.39, -77.72, -
 15 77.93, -96.87 (d, $J = 59.7$ Hz), -115.02

**EXAMPLE 61**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-

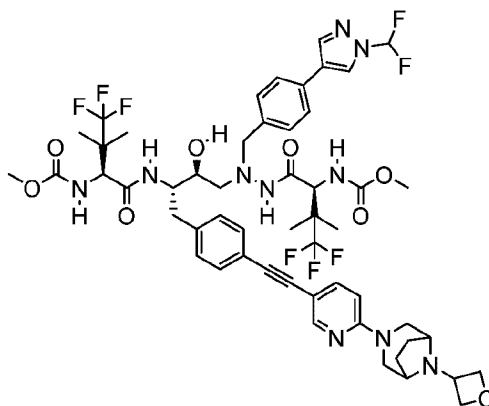
5 16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (61).

Intermediates: **I2**, **P7**, and **S7**. MS (ESI) m/z 1156.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol-
 10 d_4) δ 8.54 (d, $J = 0.7$ Hz, 1H), 8.53 (s, 2H), 8.18 (d, $J = 9.2$ Hz, 1H), 8.13 (s, 1H), 7.51 (t, $J =$
 59.7 Hz, 1H), 7.34 (d, $J = 8.2$ Hz, 2H), 7.24 (t, $J = 8.1$ Hz, 4H), 7.18 (d, $J = 9.9$ Hz, 1H), 6.82 (d,
 $J = 9.9$ Hz, 1H), 5.00 - 4.92 (m, 2H), 4.84 - 4.77 (m, 2H), 4.44 (d, $J = 9.9$ Hz, 1H), 4.31 (d, $J =$
 10.0 Hz, 1H), 4.21 - 4.07 (m, 3H), 3.79 - 3.70 (m, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.52 - 3.41 (m,
 2H), 2.96 - 2.66 (m, 4H), 2.21 (d, $J = 11.2$ Hz, 2H), 1.99 (d, $J = 9.1$ Hz, 2H), 1.17 (s, 3H), 1.14
 15 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.39, -77.72, -77.86, -
 96.87 (d, $J = 59.7$ Hz), -115.03.

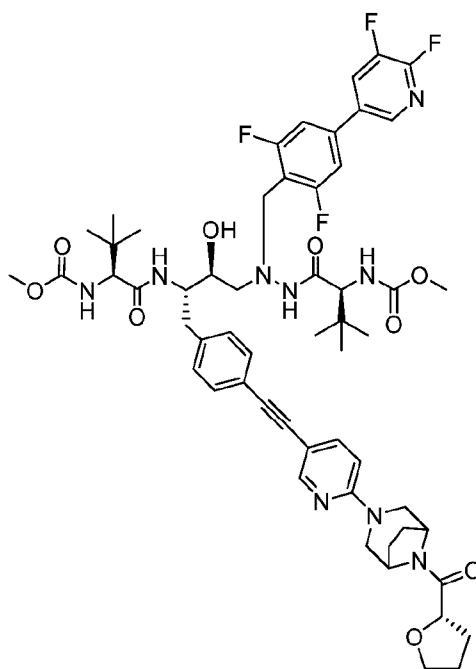
**EXAMPLE 62**

**Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-8-
(4-(((6-(1,5-dimethyl-7-(oxetan-3-yl)-9-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl)pyridin-3-
5 yl)ethynyl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-
trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (62)**

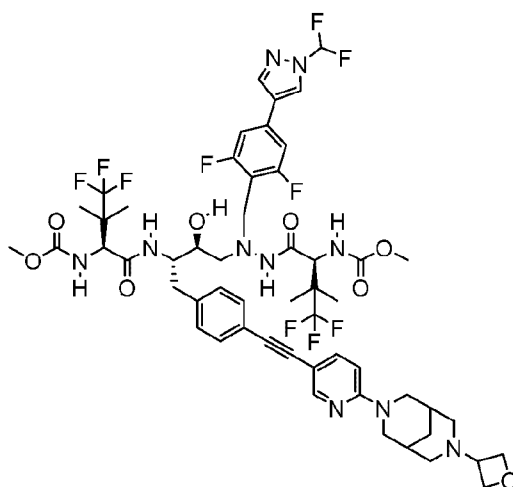
Intermediates: **I2**, **P7**, and **S37**. MS (ESI) m/z 1229.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol-
d4) δ 8.54 (d, $J = 0.8$ Hz, 1H), 8.27 (d, $J = 2.2$ Hz, 1H), 8.17 (d, $J = 9.3$ Hz, 1H), 8.12 (s, 1H),
7.98 - 7.88 (m, 1H), 7.58 (t, $J = 59.7$ Hz, 1H), 7.38 - 7.33 (m, 2H), 7.25 (dd, $J = 8.2, 5.8$ Hz, 4H),
10 7.18 (d, $J = 9.9$ Hz, 1H), 6.80 (d, $J = 9.9$ Hz, 1H), 4.83 - 4.75 (m, 1H), 4.65 (d, $J = 13.5$ Hz, 2H),
4.54 (t, $J = 6.8$ Hz, 2H), 4.43 (d, $J = 9.7$ Hz, 1H), 4.35 - 4.16 (m, 3H), 4.13 (t, $J = 11.3$ Hz, 2H),
4.02 (d, $J = 12.4$ Hz, 0H), 3.93 (d, $J = 13.1$ Hz, 1H), 3.72 (d, $J = 10.4$ Hz, 2H), 3.69 (d, $J = 2.1$
Hz, 3H), 3.66 (s, 3H), 3.53 - 3.44 (m, 1H), 2.99 - 2.71 (m, 4H), 2.47 (d, $J = 11.6$ Hz, 2H), 1.17
(s, 4H), 1.14 (s, 3H), 1.11 (s, 4H), 1.07 (s, 5H), 1.03 (s, 3H). ^{19}F NMR (377 MHz, Methanol- d_4)
15 δ -77.38, -77.71 (d, $J = 5.6$ Hz), -77.97, -96.87 (d, $J = 59.7$ Hz), -115.02.

**EXAMPLE 63**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (63). Intermediates: **I2**, **P9**, and **S3**. MS (ESI) m/z 1119.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.38 (s, 1H), 8.29 (d, J = 2.3 Hz, 1H), 8.09 (d, J = 9.7 Hz, 1H), 8.06 (s, 1H), 7.69 (dd, J = 8.9, 2.3 Hz, 1H), 7.54 (d, J = 8.1 Hz, 2H), 7.48 (t, J = 59.9 Hz, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 9.6 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 6.76 (d, J = 9.8 Hz, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.81 (dd, J = 8.3, 5.1 Hz, 2H), 4.45 - 4.31 (m, 3H), 4.25 (d, J = 9.6 Hz, 1H), 4.15 (s, 3H), 3.98 (d, J = 13.2 Hz, 1H), 3.86 (d, J = 13.0 Hz, 1H), 3.74 (d, J = 8.3 Hz, 1H), 3.68 (s, 3H), 3.60 (s, 3H), 3.37 (d, J = 13.9 Hz, 2H), 2.95 - 2.67 (m, 4H), 2.30 - 2.19 (m, 2H), 2.07 (d, J = 8.6 Hz, 2H), 1.12 (s, 3H), 1.09 (s, 3H), 1.01 (s, 3H), 0.85 (s, 3H). ^{19}F NMR (376 MHz, Methanol- d_4) δ -77.41, -77.66, -77.73, -96.57 (d, J = 59.9 Hz).

**EXAMPLE 64**

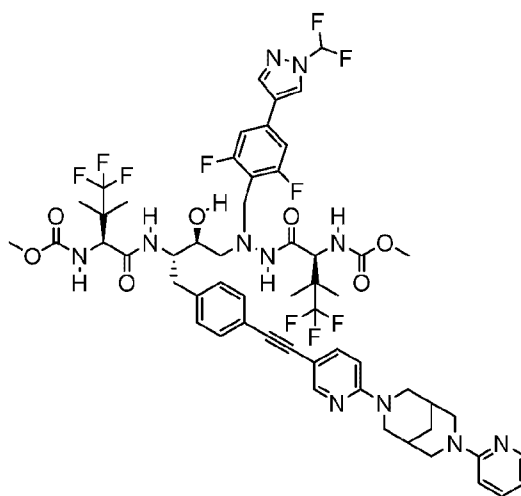
Methyl ((5S,8S,9S,14S)-5-(tert-butyl)-11-(4-(5,6-difluoropyridin-3-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-(4-((6-(8-((S)-tetrahydrofuran-2-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (64). Intermediates: **18**, and **3-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine**. MS (ESI) m/z 1086.21 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.28 (t, $J = 1.9$ Hz, 1H), 8.24 – 8.06 (m, 2H), 7.79 (q, $J = 8.3$ Hz, 2H), 7.42 – 7.14 (m, 7H), 6.99 (t, $J = 10.5$ Hz, 1H), 4.80 – 4.65 (m, 3H), 4.25 – 3.84 (m, 10H), 3.77 – 3.58 (m, 9H), 3.19 (t, $J = 12.3$ Hz, 1H), 3.02 – 2.75 (m, 6H), 2.31 – 1.76 (m, 4H), 0.87 (d, $J = 27.6$ Hz, 20H).



EXAMPLE 65

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(7-(oxetan-3-yl)-3,7-diazabicyclo[3.3.1]nonan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (65).

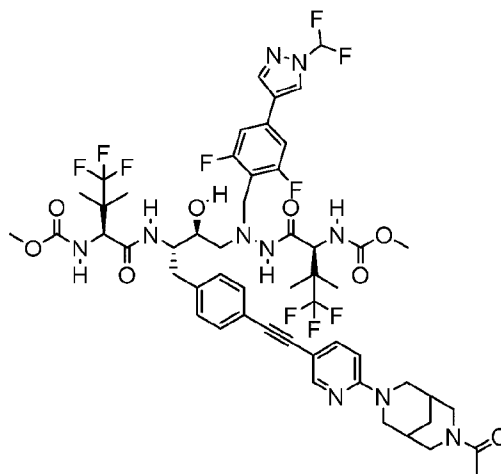
Intermediates: **I2**, **P7**, and **S41**. MS (ESI) m/z 1169.8 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.53 (s, 1H), 8.38 (s, 1H), 8.14 (d, $J = 9.5$ Hz, 1H), 8.12 (s, 1H), 7.78 (d, $J = 9.5$ Hz, 1H), 7.58 (t, $J = 59.7$ Hz, 1H), 7.35 (d, $J = 7.2$ Hz, 2H), 7.24 (t, $J = 7.8$ Hz, 4H), 7.14 (d, $J = 9.8$ Hz, 1H), 7.01 (d, $J = 8.9$ Hz, 1H), 6.79 (d, $J = 10.0$ Hz, 1H), 4.79 (t, $J = 7.8$ Hz, 2H), 4.50 - 4.24 (m, 5H), 4.19 - 4.05 (m, 2H), 3.93 (d, $J = 13.2$ Hz, 1H), 3.79 - 3.63 (m, 9H), 3.14 (d, $J = 12.3$ Hz, 2H), 3.00 - 2.72 (m, 4H), 2.46 (s, 2H), 2.13 - 1.92 (m, 2H), 1.17 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H). ^{19}F NMR (376 MHz, Methanol- d_4) δ -77.36, -77.70, -77.78, -96.88 (d, $J = 59.8$ Hz), -115.01.



EXAMPLE 66

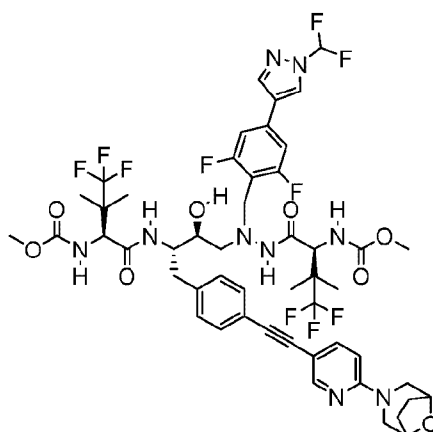
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-(((6-(7-(pyridin-2-yl)-3,7-diazabicyclo[3.3.1]nonan-3-yl)pyridin-3-yl)ethynyl)benzyl)-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (66).

Intermediates: **I2**, **P7**, and **S40**. MS (ESI) m/z 1190.7 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.52 (d, $J = 0.7$ Hz, 1H), 8.17 - 8.09 (m, 2H), 7.98 (d, $J = 2.2$ Hz, 1H), 7.81 (ddd, $J = 9.1$, 7.0, 1.8 Hz, 1H), 7.76 (ddd, $J = 6.4$, 1.8, 0.7 Hz, 1H), 7.57 (dd, $J = 9.2$, 2.3 Hz, 1H), 7.50 (t, $J = 59.7$ Hz, 1H), 7.30 (d, $J = 7.9$ Hz, 2H), 7.26 - 7.18 (m, 5H), 7.13 (d, $J = 9.9$ Hz, 1H), 6.93 (d, $J = 9.3$ Hz, 1H), 6.79 (t, $J = 6.7$ Hz, 1H), 4.50 (d, $J = 13.3$ Hz, 2H), 4.46 - 4.38 (m, 1H), 4.24 (d, $J = 13.1$ Hz, 2H), 4.20 - 4.05 (m, 2H), 3.93 (d, $J = 13.1$ Hz, 1H), 3.77 - 3.67 (m, 5H), 3.66 (s, 3H), 3.58 - 3.46 (m, 2H), 3.38 (d, $J = 13.3$ Hz, 2H), 2.96 - 2.71 (m, 4H), 2.35 (s, 2H), 2.14 (t, $J = 3.2$ Hz, 2H), 1.17 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H). ^{19}F NMR (376 MHz, Methanol- d_4) δ -77.34, -77.66, -77.97, -96.87 (d, $J = 59.6$ Hz), -115.00 (d, $J = 8.7$ Hz).

**EXAMPLE 67**

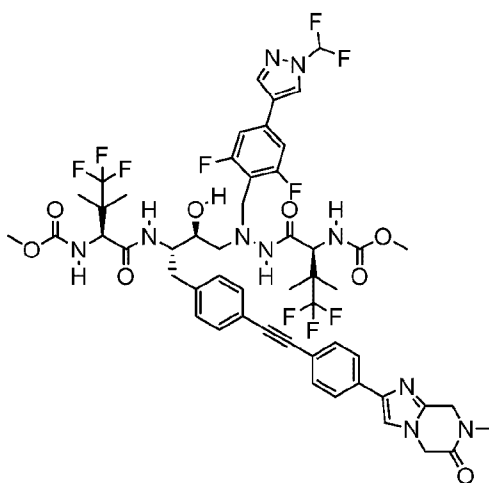
Methyl ((5S,8S,9S,14S)-8-(4-((6-(7-acetyl-3,7-diazabicyclo[3.3.1]nonan-3-yl)pyridin-3-yl)ethynyl)benzyl)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (67).

Intermediates: **I2**, **P7**, and **S39**. MS (ESI) m/z 1155.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.44 (s, 1H), 8.07 (d, $J = 9.5$ Hz, 1H), 8.03 (s, 1H), 7.99 (d, $J = 2.3$ Hz, 1H), 7.75 (d, $J = 9.4$ Hz, 1H), 7.49 (t, $J = 59.7$ Hz, 1H), 7.26 (d, $J = 7.9$ Hz, 2H), 7.20 - 7.03 (m, 5H), 6.72 (d, $J = 10.2$ Hz, 1H), 4.61 (d, $J = 13.5$ Hz, 1H), 4.38 - 4.29 (m, 3H), 4.24 - 4.17 (m, 1H), 4.04 (dt, $J = 29.4, 13.9$ Hz, 5H), 3.83 (d, $J = 13.1$ Hz, 1H), 3.66 - 3.61 (m, 1H), 3.59 (s, 3H), 3.57 (s, 3H), 3.44 - 3.26 (m, 4H), 2.87 - 2.62 (m, 6H), 2.11 (s, 3H), 1.95 (s, 3H), 1.80 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.38, -77.70, -77.88 (TFA peak), -96.88 (d, $J = 59.8$ Hz), -115.02.

**EXAMPLE 68**

Methyl ((5S,8S,9S,14S)-8-(4-((6-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (68).

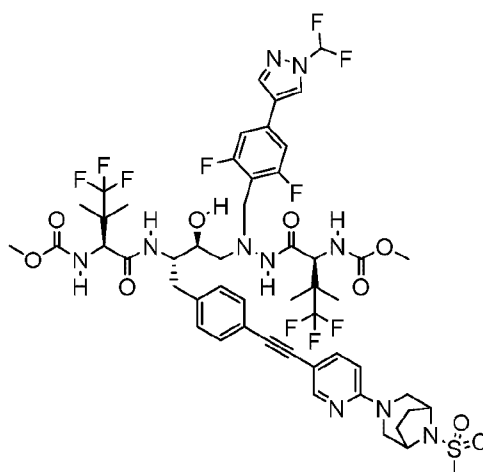
Intermediates: **I2**, **P7**, and **S43**. MS (ESI) m/z 1100.8 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.44 (s, 1H), 8.11 – 8.04 (m, 2H), 8.03 (s, 1H), 7.73 (d, J = 9.4 Hz, 1H), 7.41 (t, J = 59.8 Hz, 1H), 7.26 (d, J = 7.2 Hz, 3H), 7.15 (t, J = 7.6 Hz, 5H), 6.94 (d, J = 9.2 Hz, 1H), 4.47 – 4.38 (m, 2H), 4.37 – 4.30 (m, 1H), 4.24 – 4.18 (m, 1H), 4.12 – 3.96 (m, 2H), 3.84 (d, J = 13.1 Hz, 1H), 3.72 (d, J = 12.2 Hz, 2H), 3.66 – 3.61 (m, 1H), 3.59 (s, 3H), 3.57 (s, 3H), 3.18 – 3.12 (m, 2H), 2.86 – 2.63 (m, 5H), 1.97 – 1.85 (m, 2H), 1.81 – 1.73 (m, 2H), 1.08 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.38, -77.70, -77.94, -96.88 (d, J = 59.7 Hz), -115.02.



EXAMPLE 69

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-

- 16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((4-(7-methyl-6-oxo-5,6,7,8-**
tetrahydroimidazo[1,2-a]pyrazin-2-yl)phenyl)ethynyl)benzyl)-3,6,13-trifluoro-5-(1,1,1-
trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (69).
 Intermediates: **I2**, **P7**, and **S5**. MS (ESI) m/z 1137.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol-
 d4) δ 8.44 (s, 1H), 8.09 (d, $J = 9.4$ Hz, 1H), 8.03 (s, 1H), 7.73 (s, 1H), 7.63 (d, $J = 8.3$ Hz, 2H),
 10 7.51 (d, $J = 8.3$ Hz, 2H), 7.41 (d, $J = 59.7$ Hz, 1H), 7.32 - 7.25 (m, 2H), 7.16 (dd, $J = 8.3, 3.3$ Hz,
 4H), 7.09 (d, $J = 9.9$ Hz, 1H), 6.71 (d, $J = 10.0$ Hz, 1H), 4.39 - 4.30 (m, 1H), 4.30 - 4.17 (m,
 1H), 4.11 - 3.97 (m, 2H), 3.84 (d, $J = 13.2$ Hz, 1H), 3.68 - 3.62 (m, 1H), 3.61 (s, 3H), 3.57 (s,
 3H), 3.08 (s, 3H), 2.82 (d, $J = 7.9$ Hz, 2H), 2.78 - 2.61 (m, 2H), 1.08 (s, 3H), 1.05 (s, 3H), 1.02
 (s, 3H), 0.94 (s, 3H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.39, -77.70, -77.82, -96.87 (d, J
 15 = 59.7 Hz), -115.00.

**EXAMPLE 70**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-

16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(methylsulfonyl)-3,8-

5 **diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (70).**

Intermediates: **I2**, **P7**, and **S38**. MS (ESI) m/z 1177.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol-

d₄) δ 8.54 (s, 1H), 8.20 (d, J = 2.2 Hz, 1H), 8.12 (s, 1H), 7.73 (d, J = 9.4 Hz, 1H), 7.50 (d, J =

59.7 Hz, 1H), 7.33 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.91

10 (d, J = 9.1 Hz, 1H), 4.43 (s, 1H), 4.39 (s, 2H), 4.30 (s, 1H), 4.18 - 4.01 (m, 4H), 3.93 (d, J = 13.1

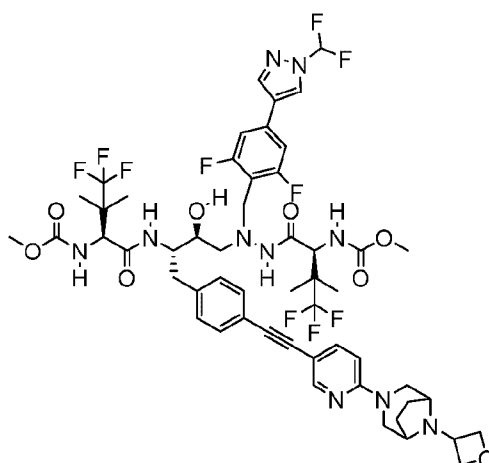
Hz, 1H), 3.76 - 3.70 (m, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.21 (d, J = 11.9 Hz, 2H), 3.04 (s, 3H),

2.95 - 2.70 (m, 4H), 2.12 - 1.99 (m, 2H), 1.86 (t, J = 7.0 Hz, 2H), 1.17 (s, 4H), 1.14 (s, 3H), 1.11

(s, 3H), 1.03 (s, 3H). ^{19}F NMR (377 MHz, Methanol-d₄) δ -77.40 (d, J = 5.6 Hz), -77.71, -77.90

, -96.88 (d, J = 59.7 Hz), -115.01.

15

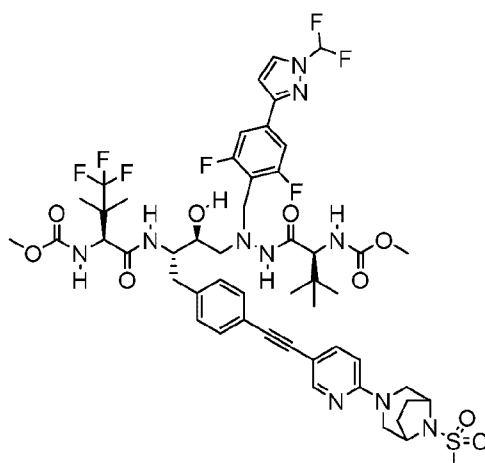
**EXAMPLE 71**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-

16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-

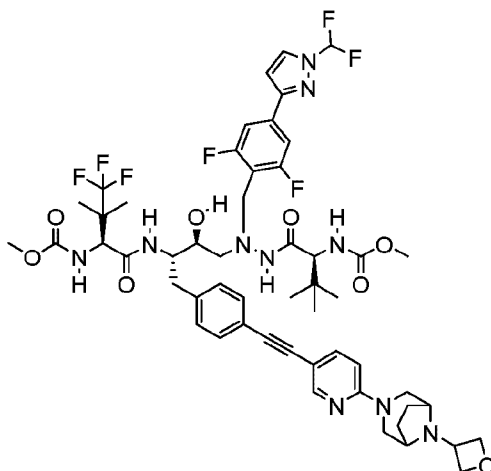
5 diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-
2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (71).

Intermediates: **I2**, **P7**, and **S3**. MS (ESI) m/z 1155.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol-
 d4) δ 8.45 (s, 1H), 8.24 - 8.18 (m, 1H), 8.08 (d, J = 9.3 Hz, 1H), 8.03 (d, J = 0.7 Hz, 1H), 7.65 -
 7.52 (m, 3H), 7.50 - 7.43 (m, 1H), 7.41 (d, J = 59.7 Hz, 1H), 7.23 (d, J = 7.9 Hz, 2H), 7.16 (d, J
 10 = 8.4 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 6.77 (d, J = 8.9 Hz, 1H), 6.71 (d, J = 10.0 Hz, 1H), 4.87
 (t, J = 7.6 Hz, 2H), 4.71 (dd, J = 8.2, 5.0 Hz, 2H), 4.34 (d, J = 9.9 Hz, 1H), 4.26 (d, J = 13.8 Hz,
 2H), 4.21 (d, J = 10.0 Hz, 1H), 4.11 - 3.97 (m, 5H), 3.83 (d, J = 13.2 Hz, 1H), 3.66 - 3.61 (m,
 1H), 3.59 (s, 3H), 3.57 (s, 3H), 3.28 (d, J = 13.9 Hz, 2H), 2.85 - 2.63 (m, 4H), 2.19 - 2.09 (m,
 2H), 2.02 - 1.95 (m, 2H), 1.08 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H). ^{19}F NMR (377
 15 MHz, Methanol- d_4) δ -77.40, -77.72, -96.87 (d, J = 59.7 Hz), -115.02.



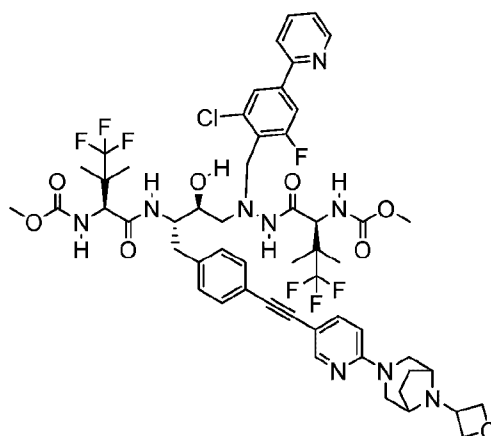
EXAMPLE 72

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-((6-(8-(methylsulfonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (72). Intermediates: **I3**, **P4**, and **S38**. MS (ESI) m/z 1123.8 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.24 - 8.14 (m, 2H), 8.10 (d, J = 2.7 Hz, 1H), 7.80 (dd, J = 9.2, 2.3 Hz, 1H), 7.53 (t, J = 59.9 Hz, 1H), 7.44 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.28 - 7.18 (m, 2H), 7.01 (d, J = 9.2 Hz, 1H), 6.93 (d, J = 2.7 Hz, 1H), 6.80 (d, J = 9.9 Hz, 1H), 4.47 - 4.38 (m, 3H), 4.17 - 4.07 (m, 2H), 4.04 (dd, J = 12.3, 2.4 Hz, 2H), 3.96 (d, J = 13.1 Hz, 1H), 3.77 - 3.72 (m, 2H), 3.69 (s, 3H), 3.65 (s, 3H), 3.27 (dd, J = 12.1, 2.5 Hz, 2H), 3.04 (s, 3H), 2.97 - 2.71 (m, 4H), 2.13 - 2.04 (m, 2H), 1.90 - 1.81 (m, 2H), 1.14 (s, 3H), 1.11 (s, 3H), 0.86 (s, 9H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.32, -77.93, -96.91 (dd, J = 59.9, 15.2 Hz), -114.77.



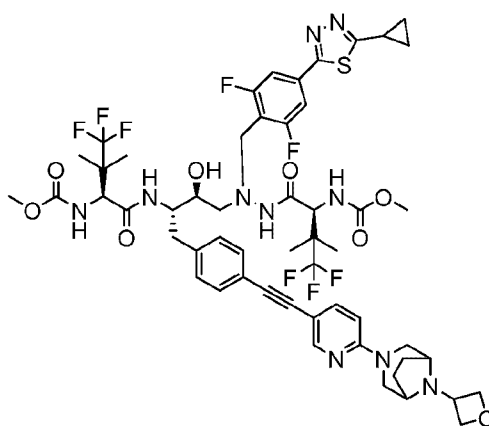
EXAMPLE 73

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (73). Intermediates: **I3**, **P4**, and **S3**. MS (ESI) m/z 1102.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.29 (d, $J = 2.2$ Hz, 1H), 8.17 (d, $J = 9.4$ Hz, 1H), 8.10 (d, $J = 2.7$ Hz, 1H), 7.71 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.53 (d, $J = 59.8$ Hz, 1H), 7.44 (d, $J = 8.3$ Hz, 2H), 7.33 (d, $J = 7.9$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 6.93 (d, $J = 2.8$ Hz, 1H), 6.91 - 6.84 (m, 1H), 4.96 (dd, $J = 8.2, 7.0$ Hz, 2H), 4.83 (dd, $J = 8.2, 5.1$ Hz, 2H), 4.61 - 4.49 (m, 1H), 4.43 (s, 1H), 4.40 - 4.29 (m, 2H), 4.19 - 4.04 (m, 4H), 3.97 (d, $J = 13.1$ Hz, 1H), 3.81 - 3.72 (m, 2H), 3.69 (s, 3H), 3.65 (s, 3H), 3.41 (dd, $J = 14.2, 1.7$ Hz, 2H), 2.99 - 2.70 (m, 4H), 2.32 - 2.18 (m, 2H), 2.13 - 1.99 (m, 2H), 1.14 (s, 3H), 1.11 (s, 3H), 0.86 (s, 9H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.35, -78.05 (TFA peak), -96.93 (dd, $J = 59.7, 14.5$ Hz), -114.79.



EXAMPLE 74

Methyl ((5S,8S,9S,14S)-11-(2-chloro-6-fluoro-4-(pyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (74). Intermediates: **I2**, **P26**, and **S3**. MS (ESI) m/z 1133.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.71 (d, J = 5.2 Hz, 1H), 8.35 - 8.27 (m, 1H), 8.19 - 8.11 (m, 2H), 8.03 (d, J = 8.0 Hz, 1H), 7.88 (s, 1H), 7.70 (dd, J = 8.9, 2.3 Hz, 1H), 7.69 - 7.64 (m, 1H), 7.63 - 7.57 (m, 1H), 7.33 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 6.87 (dd, J = 9.0, 0.8 Hz, 1H), 4.96 (dd, J = 8.2, 7.1 Hz, 2H), 4.82 (dd, J = 8.2, 5.1 Hz, 2H), 4.59 - 4.51 (m, 1H), 4.45 - 4.41 (m, 1H), 4.39 - 4.24 (m, 5H), 4.20 - 4.11 (m, 4H), 4.05 (d, J = 12.7 Hz, 1H), 3.82 - 3.73 (m, 2H), 3.69 (s, 3H), 3.63 (s, 3H), 3.44 - 3.36 (m, 2H), 2.92 (t, J = 9.0 Hz, 3H), 2.81 (dd, J = 12.6, 9.5 Hz, 1H), 2.30 - 2.18 (m, 2H), 2.12 - 2.04 (m, 2H), 1.14 (s, 6H), 1.12 (s, 3H), 1.00 (s, 3H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.30, -77.68, -78.09 (TFA peak), -112.80.

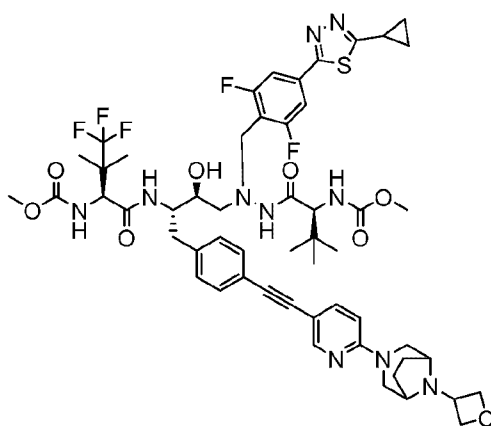


EXAMPLE 75

Methyl ((5S,8S,9S,14S)-11-(4-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-2,6-difluorobenzyl)-

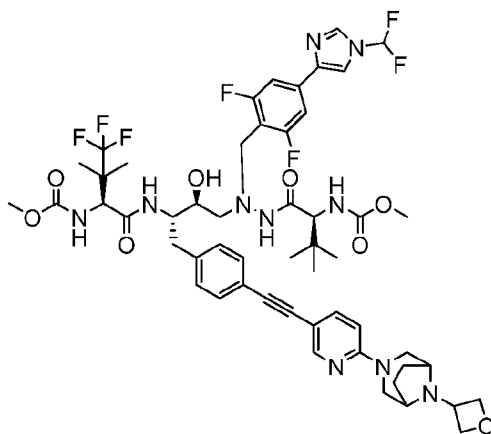
5 16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (75).

Intermediates: **I2**, **P3**, and **S3**. MS (ESI) m/z 1163.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.32 - 8.26 (m, 1H), 8.12 (d, J = 9.4 Hz, 1H), 7.70 (dd, J = 8.8, 2.3 Hz, 1H), 7.51 (d, J = 7.5 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 9.8 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 6.77 (d, J = 9.9 Hz, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.79 (s, 1H), 4.43 (d, J = 9.8 Hz, 1H), 4.35 (d, J = 14.0 Hz, 2H), 4.28 (d, J = 10.0 Hz, 1H), 4.17 (s, 5H), 3.97 (d, J = 13.2 Hz, 1H), 3.74 (d, J = 13.6 Hz, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 3.38 (d, J = 13.9 Hz, 2H), 3.02 - 2.84 (m, 3H), 2.82 - 2.74 (m, 1H), 2.53 (td, J = 8.6, 4.3 Hz, 1H), 2.27 - 2.18 (m, 2H), 2.08 (d, J = 8.6 Hz, 2H), 1.35 - 1.30 (m, 2H), 1.27 (d, J = 16.2 Hz, 0H), 1.20 - 1.13 (m, 9H), 1.12 (s, 3H), 1.03 (s, 3H). ^{19}F NMR (376 MHz, Methanol- d_4) δ -77.31, -77.67, -77.82, -113.25.



EXAMPLE 76

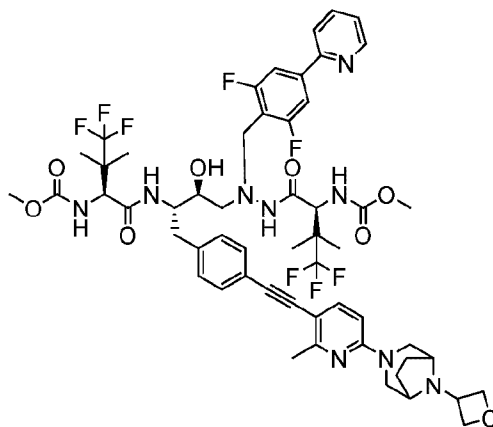
Methyl ((5S,8S,9S,14S)-11-(4-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (76). Intermediates: **I3**, **P3**, and **S3**. MS (ESI) m/z 1110.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.32 - 8.27 (m, 1H), 8.13 (d, J = 9.2 Hz, 1H), 7.70 (dd, J = 8.7, 2.3 Hz, 1H), 7.51 (d, J = 7.5 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.9 Hz, 1H), 6.78 (s, 0H), 4.96 (t, J = 7.6 Hz, 2H), 4.79 (s, 1H), 4.54 (s, 1H), 4.43 (d, J = 6.3 Hz, 1H), 4.35 (d, J = 13.9 Hz, 2H), 4.15 (s, 5H), 3.99 (d, J = 13.1 Hz, 1H), 3.74 (s, 1H), 3.69 (s, 4H), 3.65 (s, 3H), 3.38 (d, J = 13.9 Hz, 2H), 3.34 (s, 1H), 3.00 - 2.75 (m, 2H), 2.51 (dq, J = 8.5, 4.9, 4.3 Hz, 1H), 2.27 - 2.18 (m, 2H), 2.08 (d, J = 8.6 Hz, 2H), 1.36 - 1.30 (m, 2H), 1.19 - 1.13 (m, 6H), 1.12 (s, 3H), 0.85 (s, 10H). ^{19}F NMR (376 MHz, Methanol- d_4) δ -77.28, -77.92, -113.11.



EXAMPLE 77

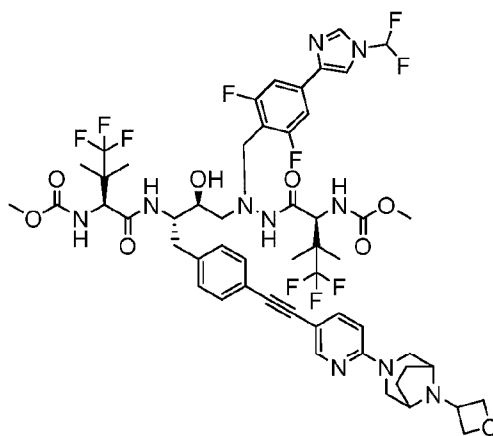
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-imidazol-4-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (77). Intermediates: **I3**, **P1**, and **S3**. MS (ESI) m/z 1102.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.30 (d, J = 2.1 Hz, 1H), 8.15 (s, 1H), 8.00 (s, 1H), 7.74 - 7.66 (m, 1H), 7.57 (s, 1H), 7.42 (s, 0H), 7.39 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 8.0 Hz, 3H), 6.86 (d, J = 8.9 Hz, 1H), 4.97 (t, J = 7.6 Hz, 3H), 4.80 (d, J = 5.2 Hz, 1H), 4.43 (d, J = 9.8 Hz, 1H), 4.35 (d, J = 14.1 Hz, 2H), 4.19 - 4.08 (m, 5H), 3.96 (d, J = 13.2 Hz, 1H), 3.76 (s, 1H), 3.69 (s, 4H), 3.65 (s, 3H), 3.38 (d, J = 13.9 Hz, 3H), 2.90 (d, J = 8.1 Hz, 2H), 2.81 (s, 1H), 2.22 (s, 2H), 2.08 (d, J = 8.7 Hz, 2H), 1.13 (d, J = 14.1 Hz, 8H), 0.86 (s, 12H). ^{19}F NMR (376 MHz, Methanol- d_4) δ -77.36, -77.93, -94.99 (d, J = 60.0 Hz), -115.00

15

**EXAMPLE 78**

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((2-methyl-6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (78). Intermediates: **I2**, **P28**, and **S45**. MS (ESI) m/z 1131.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.65 (d, J = 5.0 Hz, 1H), 8.14

(d, J = 9.3 Hz, 1H), 7.98 - 7.85 (m, 2H), 7.61 (t, J = 8.1 Hz, 3H), 7.47 - 7.38 (m, 1H), 7.33 (d, J = 7.8 Hz, 3H), 7.22 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 9.9 Hz, 1H), 6.77 (d, J = 9.8 Hz, 1H), 6.67 (d, J = 8.7 Hz, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.42 (dd, J = 25.4, 11.7 Hz, 2H), 4.33 - 4.27 (m, 1H), 4.22 - 4.10 (m, 4H), 3.98 (d, J = 13.0 Hz, 1H), 3.73 (s, 1H), 3.68 (s, 4H), 3.63 (s, 3H), 3.35 (d, J = 14.0 Hz, 2H), 2.97 - 2.86 (m, 3H), 2.84 - 2.75 (m, 1H), 2.56 (s, 4H), 2.25 - 2.16 (m, 2H), 2.13 - 2.01 (m, 2H), 1.28 (d, J = 8.8 Hz, 0H), 1.16 (d, J = 2.7 Hz, 7H), 1.13 (s, 4H), 1.03 (s, 3H). ¹⁹F NMR (376 MHz, Methanol-d₄) δ -77.35, -77.68, -114.72.



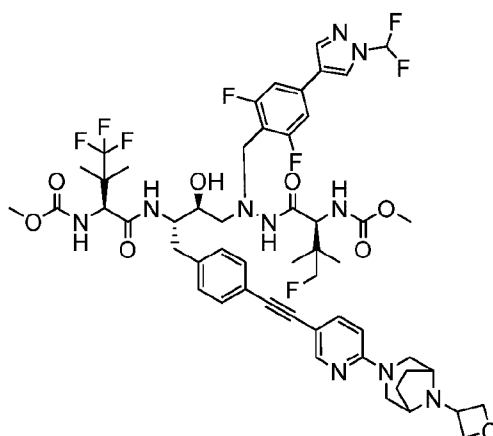
10

EXAMPLE 79

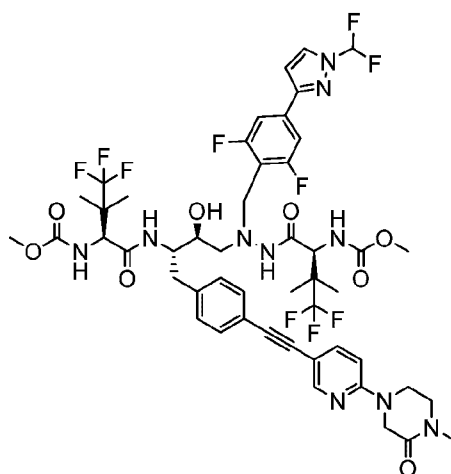
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-imidazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (79).

15 Intermediates: **I2**, **P1**, and **S3**. MS (ESI) m/z 1156.0 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.32 - 8.28 (m, 1H), 8.15 (d, J = 1.2 Hz, 1H), 8.13 (s, 0H), 8.00 (d, J = 1.3 Hz, 1H), 7.73 (s, 0H), 7.70 (dd, J = 8.8, 2.3 Hz, 1H), 7.58 (s, 1H), 7.43 (s, 0H), 7.39 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 9.8 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 6.77 (d, J = 10.0 Hz, 0H), 4.97 (t, J = 7.6 Hz, 2H), 4.82 - 4.78 (m, 2H), 4.53 (s, 1H), 4.44 (d, J = 6.5 Hz, 1H), 4.39 - 4.28 (m, 3H), 4.13 (d, J = 15.7 Hz, 4H), 3.94 (d, J = 13.3 Hz, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 3.38 (d, J = 13.9 Hz, 2H), 2.97 - 2.72 (m, 6H), 2.27 - 2.19 (m, 2H), 2.08 (d, J = 8.6 Hz, 2H), 1.21 (t, J = 7.3 Hz, 4H), 1.16 (d, J = 8.4 Hz, 6H), 1.11 (s, 3H), 1.03 (s, 3H). ¹⁹F NMR (376 MHz, Methanol-d₄) δ -74.51, -76.39, -77.39, -77.71, -77.89, -94.98 (d, J = 60.0 Hz), -97.37 (d, J = 59.1 Hz), -115.13

25

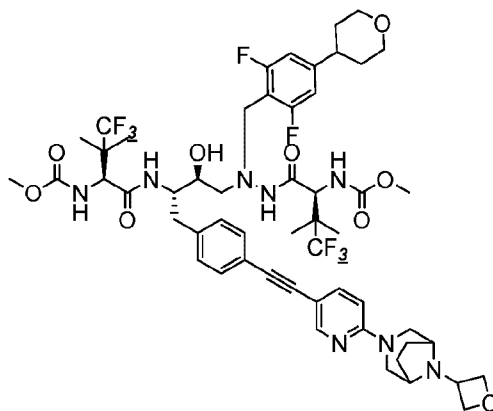
**EXAMPLE 80**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16-fluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (80). Intermediates: **I6**, **P7**, and **S3**. MS (ESI) m/z 1119.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.54 (d, J = 0.7 Hz, 1H), 8.32 - 8.27 (m, 1H), 8.17 (d, J = 9.4 Hz, 1H), 8.12 (s, 1H), 7.88 - 7.73 (m, 0H), 7.70 (dd, J = 8.8, 2.3 Hz, 1H), 7.65 (s, 0H), 7.51 (s, 1H), 7.38 - 7.30 (m, 2H), 7.24 (dd, J = 16.7, 8.2 Hz, 4H), 6.86 (d, J = 9.0 Hz, 1H), 6.81 (d, J = 9.9 Hz, 1H), 4.96 (dd, J = 8.1, 7.0 Hz, 2H), 4.84 - 4.77 (m, 2H), 4.47 - 4.41 (m, 1H), 4.36 (d, J = 13.7 Hz, 2H), 4.22 (d, J = 9.2 Hz, 1H), 4.18 - 4.03 (m, 5H), 4.00 (s, 1H), 3.98 - 3.91 (m, 2H), 3.71 (s, 0H), 3.69 (s, 3H), 3.66 (s, 3H), 3.37 (d, J = 13.8 Hz, 2H), 3.04 (q, J = 7.4 Hz, 1H), 2.99 (d, J = 0.5 Hz, 0H), 2.90 (d, J = 9.1 Hz, 2H), 2.86 (d, J = 0.7 Hz, 0H), 2.79 (d, J = 9.6 Hz, 2H), 2.28 - 2.19 (m, 2H), 2.11 - 2.02 (m, 2H), 1.29 (t, J = 7.3 Hz, 1H), 1.13 (d, J = 10.8 Hz, 6H), 1.02 (t, J = 7.4 Hz, 0H), 0.93 - 0.84 (m, 6H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.38 , -77.88 , -96.88 (d, J = 59.7 Hz), -114.92

**EXAMPLE 81**

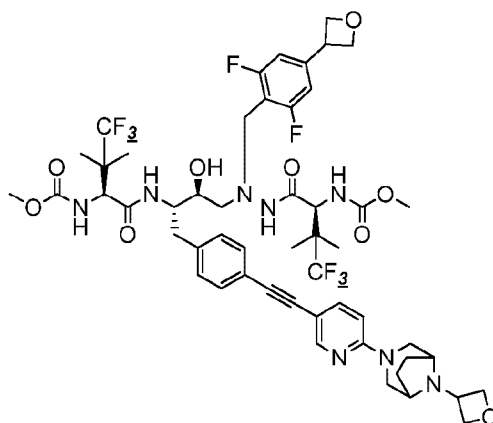
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(4-methyl-3-oxopiperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (81). Intermediates: **I2**, **P4**, and **S47**. MS (ESI) m/z 1102.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.25 - 8.21 (m, 1H), 8.16 (d, J = 9.3 Hz, 1H), 8.10 (d, J = 2.8 Hz, 1H), 7.77 (dd, J = 9.0, 2.3 Hz, 1H), 7.53 (s, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 9.9 Hz, 1H), 6.98 - 6.91 (m, 2H), 6.80 (d, J = 9.9 Hz, 1H), 4.48 - 4.41 (m, 1H), 4.36 - 4.27 (m, 1H), 4.20 (s, 2H), 4.14 (d, J = 13.0 Hz, 2H), 3.96 (s, 1H), 3.95 - 3.87 (m, 3H), 3.73 (s, 2H), 3.68 (d, J = 11.7 Hz, 6H), 3.60 - 3.51 (m, 2H), 3.04 (s, 3H), 2.94 - 2.84 (m, 3H), 2.84 - 2.73 (m, 1H), 1.20 - 1.08 (m, 9H), 1.03 (s, 3H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.38, -77.71, -96.96 (dd, J = 59.8, 19.5 Hz), -114.92.

15



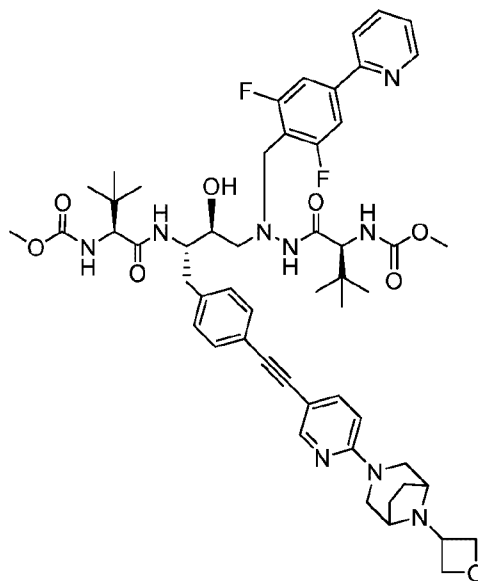
EXAMPLE 82

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(tetrahydro-2H-pyran-4-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (82). Intermediates: **I2**, **P33**, and **S3**. MS (ESI) m/z 1123.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.30 (dd, $J = 2.4, 0.7$ Hz, 1H), 8.16 (d, $J = 9.4$ Hz, 1H), 7.70 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.33 (d, $J = 7.9$ Hz, 2H), 7.21 (d, $J = 8.3$ Hz, 2H), 6.92 - 6.71 (m, 3H), 4.97 (dd, $J = 8.1, 7.2$ Hz, 2H), 4.83 - 4.74 (m, 2H), 4.58 - 4.23 (m, 4H), 4.17 - 3.96 (m, 8H), 3.90 (d, $J = 13.4$ Hz, 1H), 3.74 - 3.58 (m, 8H), 3.54 (td, $J = 11.2, 3.9$ Hz, 2H), 3.39 (d, $J = 13.8$ Hz, 2H), 3.03 - 2.60 (m, 5H), 2.36 - 2.17 (m, 2H), 2.20 - 2.03 (m, 4H), 1.93 - 1.83 (m, 1H), 1.80 - 1.48 (m, 5H), 1.29 (d, $J = 3.8$ Hz, 1H), 1.20 - 1.05 (m, 11H), 0.95 (d, $J = 41.7$ Hz, 4H).

**EXAMPLE 83**

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(oxetan-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (83). Intermediates: **I2**, **P32**, and **S3**. MS (ESI) m/z 1095.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.28 (dd, $J = 2.3, 0.7$ Hz, 1H), 8.15 (d, $J = 9.4$ Hz, 1H), 7.69 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.20 (d, $J = 8.1$ Hz, 2H), 6.99 (d, $J = 8.3$ Hz, 2H), 6.92 - 6.70 (m, 2H), 5.05 (dd, $J = 8.3, 6.1$ Hz, 3H), 4.95 (dd, $J = 8.2, 7.0$ Hz, 3H), 4.80 (dd, $J = 8.0, 4.8$ Hz, 3H), 4.67 (t, $J = 6.3$ Hz, 2H), 4.50 - 4.17 (m, 4H), 4.14 (d, $J =$

4.3 Hz, 3H), 3.68 (d, $J = 1.5$ Hz, 7H), 3.38 (dd, $J = 14.2, 1.7$ Hz, 3H), 3.00 - 2.68 (m, 2H), 2.06 (d, $J = 9.0$ Hz, 1H), 1.73 (d, $J = 7.2$ Hz, 0H), 1.64 - 1.49 (m, 1H), 1.42 - 1.25 (m, 25H), 1.17 - 1.05 (m, 11H), 1.01 (s, 3H), 0.96 (d, $J = 6.6$ Hz, 2H), 0.92 - 0.80 (m, 24H).

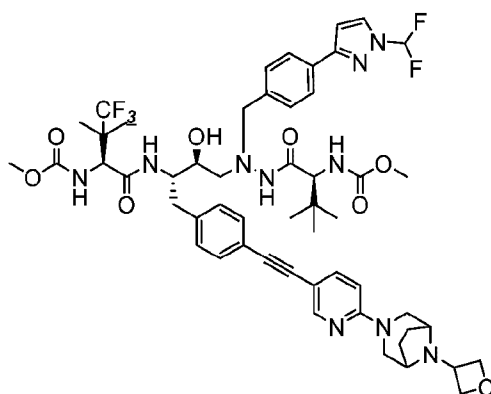


5

EXAMPLE 84

Methyl ((5S,8S,9S,14S)-5-(tert-butyl)-11-(2,6-difluoro-4-(pyridin-2-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (84).

Intermediates: **11**, **P28**, and **S3**. MS (ESI) m/z 1009.35 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.65 (d, $J = 4.9$ Hz, 1H), 8.34 - 8.25 (m, 1H), 8.01 - 7.87 (m, 2H), 7.83 (d, $J = 9.4$ Hz, 1H), 7.70 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.59 (d, $J = 8.6$ Hz, 2H), 7.44 (dd, $J = 7.0, 5.0$ Hz, 1H), 7.33 (d, $J = 7.8$ Hz, 2H), 7.24 (d, $J = 7.9$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 1H), 4.96 (t, $J = 7.6$ Hz, 2H), 4.84 - 4.79 (m, 1H), 4.53 (s, 1H), 4.35 (d, $J = 13.9$ Hz, 2H), 4.15 (s, 6H), 4.00 (d, $J = 13.1$ Hz, 1H), 3.90 (s, 1H), 3.80 - 3.58 (m, 9H), 3.40 (s, 1H), 3.03 - 2.80 (m, 5H), 2.34 - 2.20 (m, 3H), 2.07 (d, $J = 8.6$ Hz, 2H), 0.87 (d, $J = 24.4$ Hz, 19H).

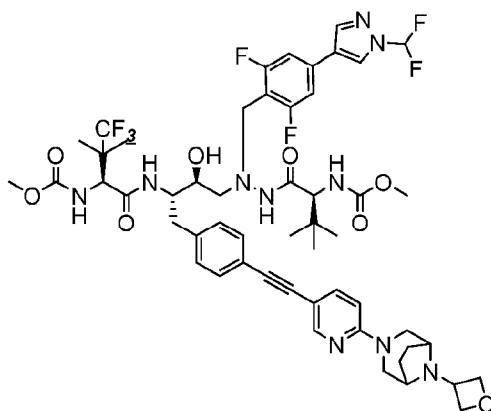


EXAMPLE 85

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)benzyl)-9-hydroxy-

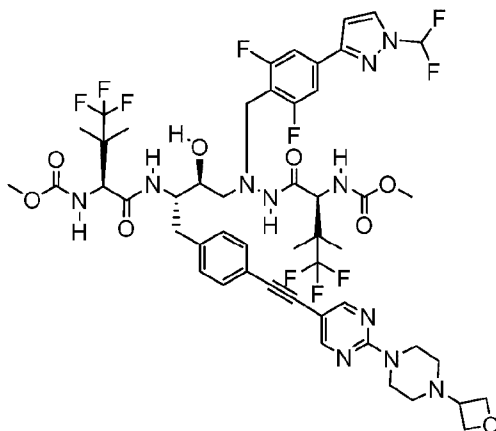
15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (85). Intermediates: **I3**, **P6**, and **S3**. MS (ESI) m/z 1066.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.25 (d, $J = 2.3$ Hz, 1H), 8.13 – 8.04 (m, 2H), 7.83 – 7.74 (m, 4H), 7.47 (d, $J = 8.2$ Hz, 3H), 7.35 – 7.30 (m, 3H), 7.23 (d, $J = 8.2$ Hz, 3H), 6.99 (d, $J = 9.1$ Hz, 2H), 6.86 (d, $J = 2.7$ Hz, 1H), 4.58 – 4.49 (m, 2H), 4.35 (t, $J = 4.9$ Hz, 1H), 4.31 – 4.23 (m, 3H), 4.17 (d, $J = 3.8$ Hz, 3H), 4.03 – 3.89 (m, 2H), 3.81 (s, 1H), 3.67 (s, 5H), 3.62 – 3.49 (m, 6H), 2.95 – 2.74 (m, 3H), 2.30 – 2.23 (m, 2H), 2.07 (d, $J = 8.8$ Hz, 2H), 1.02 (d, $J = 34.0$ Hz, 6H), 0.74 (s, 10H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.58, -96.21 (d, $J = 59.7$ Hz).

15



EXAMPLE 86

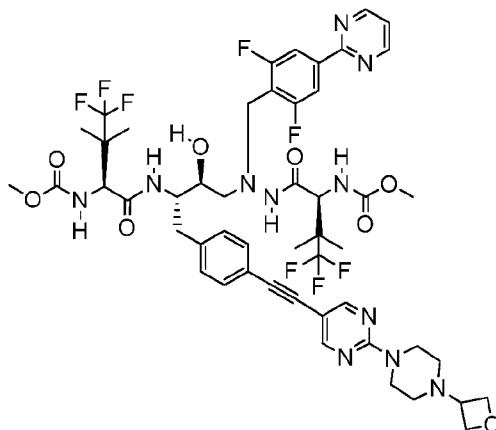
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (86) Intermediates: **I3**, **P7**, and **S3**. MS (ESI) m/z 1066.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.53 (d, $J = 0.7$ Hz, 1H), 8.16 (d, $J = 9.3$ Hz, 1H), 8.11 (d, $J = 0.6$ Hz, 1H), 7.72 – 7.69 (m, 1H), 7.37 – 7.30 (m, 3H), 7.27 – 7.19 (m, 5H), 6.87 (dd, $J = 9.1, 0.8$ Hz, 1H), 6.80 (d, $J = 9.9$ Hz, 1H), 4.98 – 4.94 (m, 2H), 4.84 – 4.81 (m, 2H), 4.46 – 4.41 (m, 1H), 4.38 – 4.31 (m, 2H), 4.18 – 4.07 (m, 5H), 3.95 (d, $J = 13.2$ Hz, 1H), 3.76 (s, 1H), 3.67 (d, $J = 15.6$ Hz, 7H), 3.40 (dd, $J = 14.2, 1.8$ Hz, 2H), 2.93 – 2.87 (m, 2H), 2.80 (s, 2H), 2.26 – 2.20 (m, 2H), 2.10 – 2.04 (m, 2H), 1.13 (d, $J = 11.9$ Hz, 7H), 0.86 (s, 11H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -78.10, -96.87 (d, $J = 59.7$ Hz), -114.89.



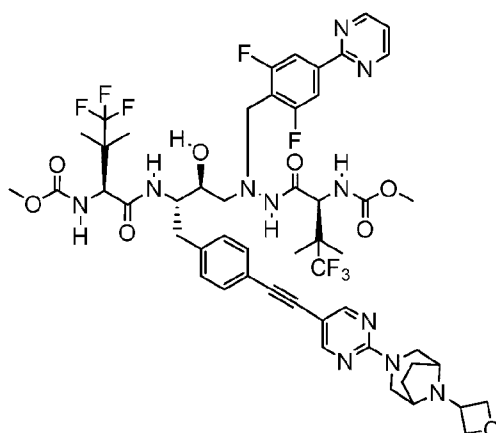
15

EXAMPLE 87

methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((2-(4-(oxetan-3-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (87). Intermediates: **I2**, **P4**, and **S49**. MS (ESI) m/z 1130.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 1H), 8.20 - 8.01 (m, 1H), 7.67 (s, 0H), 7.52 (s, 0H), 7.44 (d, $J = 8.2$ Hz, 1H), 7.40 - 7.29 (m, 1H), 7.23 (d, $J = 8.2$ Hz, 1H), 7.09 (d, $J = 9.9$ Hz, 0H), 6.93 (d, $J = 2.8$ Hz, 1H), 6.77 (d, $J = 9.9$ Hz, 0H), 4.90 (t, $J = 7.7$ Hz, 1H), 4.52 - 4.27 (m, 2H), 4.14 (d, $J = 13.5$ Hz, 2H), 3.94 (d, $J = 13.1$ Hz, 1H), 3.67 (d, $J = 10.3$ Hz, 4H), 2.98 - 2.72 (m, 2H), 1.28 - 1.06 (m, 5H), 1.02 (s, 1H).

**EXAMPLE 88**

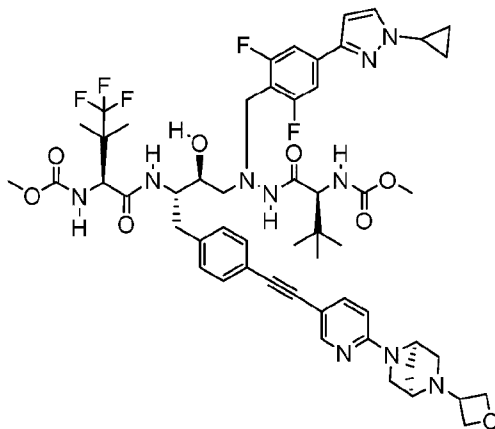
Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyrimidin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((2-(4-(oxetan-3-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (88). Intermediates: **I2**, **P16**, and **S49**. MS (ESI) m/z 1092.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.86 (d, $J = 4.8$ Hz, 1H), 8.52 (s, 1H), 8.14 (d, $J = 9.3$ Hz, 0H), 7.97 (d, $J = 8.6$ Hz, 1H), 7.40 (t, $J = 4.9$ Hz, 1H), 7.34 (d, $J = 7.9$ Hz, 1H), 7.23 (d, $J = 8.2$ Hz, 1H), 7.08 (d, $J = 10.0$ Hz, 0H), 6.78 (d, $J = 9.9$ Hz, 0H), 4.90 (t, $J = 7.7$ Hz, 1H), 4.51 - 4.26 (m, 2H), 4.25 - 4.09 (m, 2H), 3.98 (d, $J = 13.2$ Hz, 1H), 3.67 (d, $J = 8.1$ Hz, 3H), 3.26 (s, 2H), 2.99 - 2.75 (m, 2H), 2.02 (s, 0H), 1.24 - 1.07 (m, 5H), 1.02 (s, 1H).

**EXAMPLE 89**

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyrimidin-2-yl)benzyl)-16,16,16-trifluoro-9-

hydroxy-15,15-dimethyl-8-(4-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (89). Intermediates: **I2**, **P16**, and **S7**. MS (ESI) m/z 1119.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.86 (d, J = 4.8 Hz, 1H), 8.52 (s, 1H), 8.15 (d, J = 9.4 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.40 (t, J = 4.9 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 9.9 Hz, 0H), 6.78 (d, J = 9.9 Hz, 0H), 4.96 (t, J = 7.6 Hz, 1H), 4.82 - 4.70 (m, 2H), 4.43 (d, J = 9.9 Hz, 0H), 4.30 (d, J = 10.0 Hz, 1H), 4.24 - 4.06 (m, 2H), 3.98 (d, J = 13.1 Hz, 1H), 3.68 (d, J = 8.7 Hz, 4H), 3.46 (d, J = 14.7 Hz, 1H), 2.99 - 2.70 (m, 2H), 2.27 - 2.10 (m, 1H), 1.99 (d, J = 8.7 Hz, 1H), 1.19 - 1.05 (m, 5H), 1.02 (s, 2H).

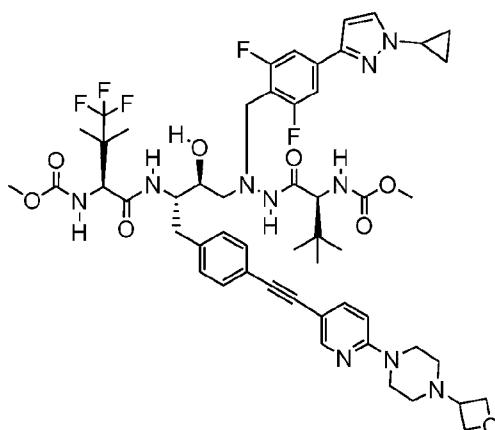
10



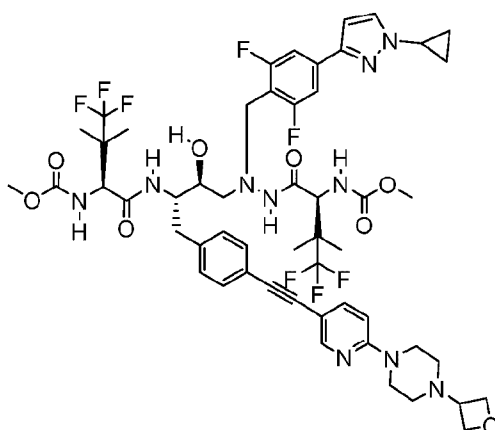
EXAMPLE 90

Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(4-((6-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (90). Intermediates: **I3**, **P13**, and **S6**. MS (ESI) m/z 1078.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.25 (d, J = 2.2 Hz, 1H), 8.15 (d, J = 9.4 Hz, 1H), 7.70 (dd, J = 11.1, 2.3 Hz, 2H), 7.43 - 7.27 (m, 4H), 7.21 (d, J = 7.9 Hz, 2H), 6.77 (d, J = 9.9 Hz, 0H), 6.73 - 6.58 (m, 2H), 5.05 (s, 1H), 5.00 - 4.88 (m, 2H), 4.71 (dd, J = 8.4, 4.6 Hz, 1H), 4.64 - 4.54 (m, 2H), 4.47 (d, J = 31.7 Hz, 2H), 4.10 (d, J = 13.2 Hz, 2H), 3.95 (d, J = 13.2 Hz, 1H), 3.82 - 3.56 (m, 13H), 3.33 (s, 1H), 2.89 (d, J = 8.9 Hz, 2H), 2.33 (s, 2H), 1.21 - 0.99 (m, 11H), 0.86 (s, 10H).

20

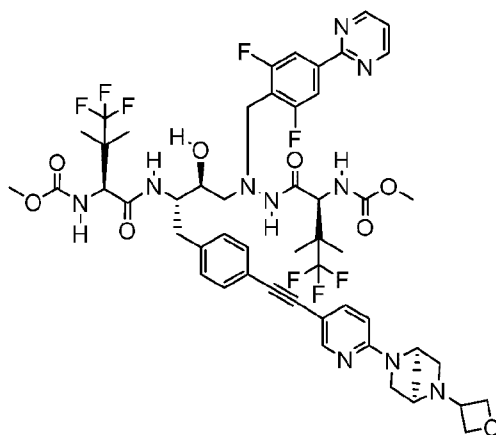
**EXAMPLE 91**

Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(4-((6-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (91). Intermediates: **I3**, **P13**, and **S48**. MS (ESI) m/z 1066.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.30 (d, $J = 2.2$ Hz, 1H), 8.15 (d, $J = 9.4$ Hz, 1H), 7.79 - 7.63 (m, 2H), 7.33 (dd, $J = 8.2, 5.2$ Hz, 4H), 7.21 (d, $J = 8.0$ Hz, 2H), 6.95 (d, $J = 8.9$ Hz, 1H), 6.77 (d, $J = 10.0$ Hz, 1H), 6.63 (d, $J = 2.4$ Hz, 1H), 4.91 (t, $J = 7.7$ Hz, 2H), 4.54 - 4.33 (m, 2H), 4.18 - 4.02 (m, 2H), 4.03 - 3.85 (m, 5H), 3.83 - 3.58 (m, 10H), 2.89 (d, $J = 9.3$ Hz, 2H), 1.27 (d, $J = 13.9$ Hz, 1H), 1.21 - 1.00 (m, 12H), 0.86 (s, 10H).

**EXAMPLE 92**

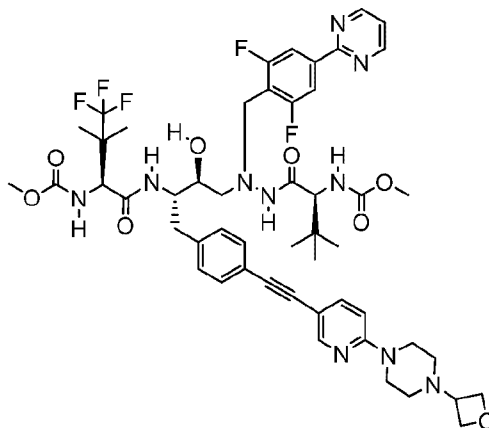
Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-

16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-((4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (92). Intermediates: **I2**, **P13**, and **S48**. MS (ESI) m/z 1119.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.29 (d, J = 2.2 Hz, 1H), 8.14 (d, J = 9.4 Hz, 1H), 7.70 (dd, J = 9.2, 2.3 Hz, 2H), 7.64 - 7.51 (m, 0H), 7.33 (dd, J = 8.4, 4.0 Hz, 5H), 7.21 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 9.8 Hz, 1H), 6.94 (d, J = 8.9 Hz, 1H), 6.76 (d, J = 10.0 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 5.48 (s, 1H), 4.91 (dd, J = 8.3, 7.0 Hz, 3H), 4.51 - 4.38 (m, 2H), 4.31 (d, J = 9.9 Hz, 1H), 4.13 (dd, J = 15.3, 11.1 Hz, 3H), 3.93 (d, J = 13.0 Hz, 2H), 3.79 - 3.62 (m, 10H), 3.58 - 3.43 (m, 0H), 2.99 - 2.66 (m, 5H), 1.27 (d, J = 13.9 Hz, 1H), 1.21 - 0.97 (m, 19H).

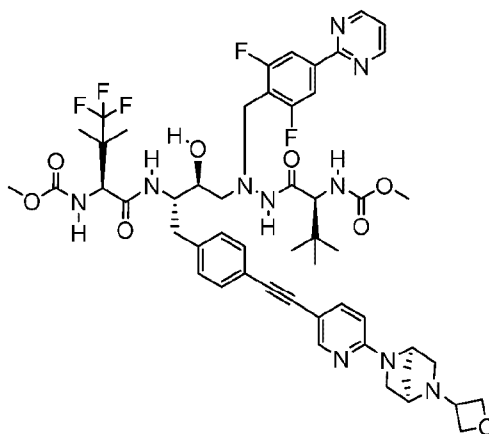


EXAMPLE 93

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyrimidin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (93). Intermediates: **I2**, **P16**, and **S6**. MS (ESI) m/z 1103.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.86 (d, J = 4.8 Hz, 1H), 8.28 - 8.20 (m, 0H), 8.14 (d, J = 9.4 Hz, 0H), 7.96 (d, J = 8.5 Hz, 1H), 7.71 (dd, J = 8.8, 2.3 Hz, 1H), 7.40 (t, J = 4.9 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 6.74 - 6.65 (m, 1H), 5.05 (d, J = 2.0 Hz, 1H), 5.01 - 4.90 (m, 1H), 4.72 (dd, J = 8.4, 4.8 Hz, 1H), 4.58 - 4.49 (m, 1H), 4.43 (t, J = 5.0 Hz, 0H), 4.40 - 4.26 (m, 1H), 4.18 (d, J = 12.8 Hz, 1H), 3.98 (d, J = 13.1 Hz, 1H), 3.87 - 3.63 (m, 5H), 3.34 (s, 0H), 3.03 - 2.75 (m, 2H), 2.33 (s, 1H), 1.13 (d, J = 14.3 Hz, 5H), 1.02 (s, 2H).

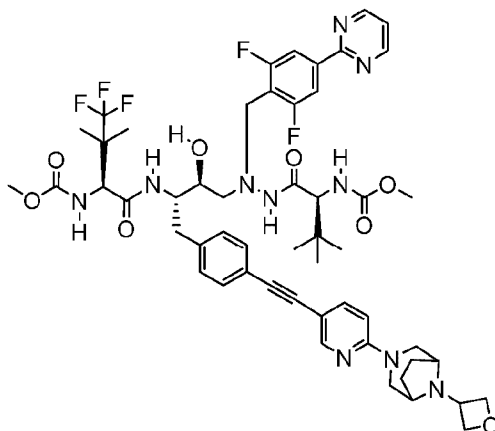
**EXAMPLE 94**

methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyrimidin-2-yl)benzyl)-9-hydroxy-15,15-
 5 dimethyl-8-((6-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-
 5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-
 yl)carbamate (**94**). Intermediates: **I3**, **P16**, and **S48**. MS (ESI) m/z 1037.6 $[M+H]^+$. 1H NMR
 (400 MHz, Methanol- d_4) δ 8.86 (d, $J = 4.8$ Hz, 1H), 8.29 (d, $J = 2.2$ Hz, 0H), 7.97 (d, $J = 8.9$
 Hz, 1H), 7.70 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.39 (t, $J = 4.9$ Hz, 1H), 7.32 (d, $J = 7.8$ Hz, 1H), 7.21
 10 (d, $J = 7.9$ Hz, 1H), 6.95 (d, $J = 8.9$ Hz, 1H), 6.77 (d, $J = 9.9$ Hz, 0H), 4.84 (s, 15H), 4.57 - 4.31
 (m, 1H), 4.16 (d, $J = 14.1$ Hz, 1H), 3.98 (d, $J = 35.4$ Hz, 2H), 3.76 (s, 1H), 3.67 (d, $J = 14.2$ Hz,
 4H), 3.04 - 2.69 (m, 2H), 2.02 (s, 1H), 1.27 (d, $J = 13.9$ Hz, 1H), 1.12 (d, $J = 14.5$ Hz, 3H), 0.85
 (s, 5H).



EXAMPLE 95

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyrimidin-2-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-(4-(((6-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (95). Intermediates: **I3**, **P16**, and **S6**. MS (ESI) m/z 1050.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.86 (d, $J = 4.9$ Hz, 1H), 8.24 (d, $J = 2.1$ Hz, 0H), 8.15 (d, $J = 9.3$ Hz, 0H), 7.97 (d, $J = 8.7$ Hz, 1H), 7.70 (dd, $J = 8.8, 2.2$ Hz, 1H), 7.39 (t, $J = 4.9$ Hz, 1H), 7.32 (d, $J = 7.8$ Hz, 1H), 7.21 (d, $J = 7.9$ Hz, 1H), 6.78 (d, $J = 9.8$ Hz, 0H), 6.67 (d, $J = 8.8$ Hz, 1H), 5.05 (s, 0H), 4.98 - 4.85 (m, 1H), 4.71 (dd, $J = 8.4, 4.7$ Hz, 1H), 4.66 - 4.55 (m, 1H), 4.53 - 4.41 (m, 1H), 4.16 (d, $J = 13.7$ Hz, 1H), 4.00 (d, $J = 13.1$ Hz, 1H), 3.87 - 3.61 (m, 6H), 3.30 (p, $J = 1.6$ Hz, 4H), 3.00 - 2.74 (m, 2H), 2.33 (s, 1H), 1.12 (d, $J = 14.5$ Hz, 3H), 0.85 (s, 5H).

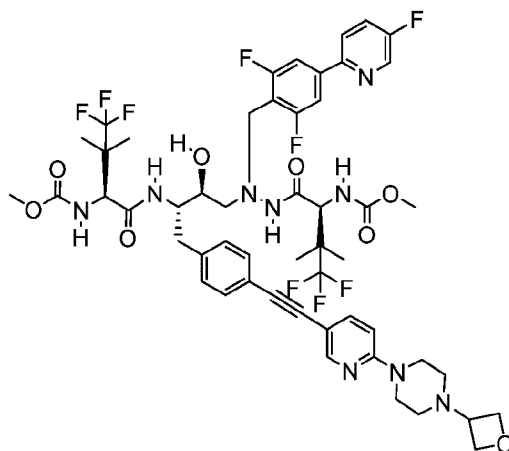


15

EXAMPLE 96

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyrimidin-2-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-(4-(((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (96). Intermediates: **I3**, **P16**, and **S3**. MS (ESI) m/z 1063.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.86 (dd, $J = 4.9, 0.8$ Hz, 1H), 8.29 (d, $J = 2.2$ Hz, 0H), 8.15 (d, $J = 9.4$ Hz, 0H), 7.97 (d, $J = 8.6$ Hz, 1H), 7.69 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.40 (t, $J = 4.9$ Hz, 1H), 7.32 (d, $J = 7.8$ Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 6.85 (d, $J = 8.9$ Hz, 1H), 6.77 (d, $J = 10.0$ Hz, 0H), 4.96 (t, $J = 7.6$ Hz, 1H), 4.83 (s, 20H), 4.39 (dd, $J = 34.8, 11.8$ Hz, 2H), 4.16 (d, $J = 14.7$ Hz, 2H), 4.01 (d, $J = 13.1$ Hz, 1H), 3.84 - 3.60 (m, 4H), 3.37 (d, $J =$

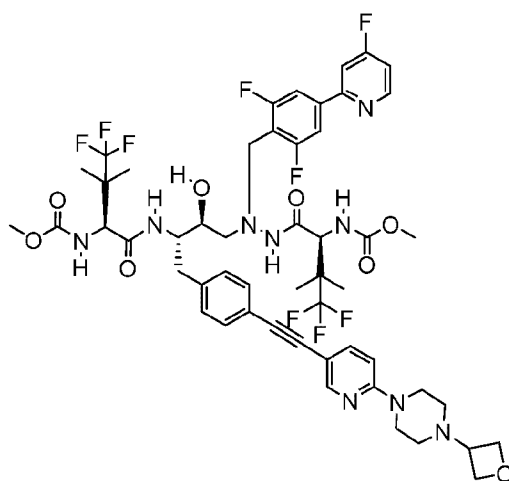
13.9 Hz, 1H), 3.01 - 2.73 (m, 2H), 2.33 - 2.17 (m, 1H), 2.07 (d, J = 8.6 Hz, 1H), 1.12 (d, J = 14.3 Hz, 3H), 0.85 (s, 5H).



EXAMPLE 97

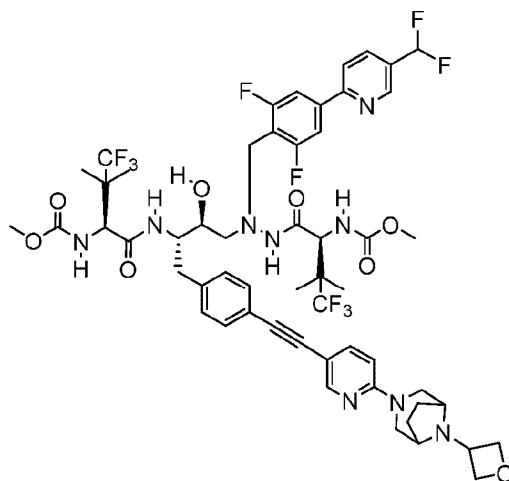
Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(5-fluoropyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (97). Intermediates: **I2**, **P14**, and **S48**. MS (ESI) m/z

1108.4 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.54 (d, J = 2.9 Hz, 1H), 8.29 (d, J = 2.2 Hz, 1H), 8.14 (d, J = 9.3 Hz, 1H), 7.95 (dd, J = 8.9, 4.2 Hz, 1H), 7.78 - 7.51 (m, 4H), 7.32 (d, J = 7.8 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 10.0 Hz, 1H), 6.94 (d, J = 8.9 Hz, 1H), 6.77 (d, J = 9.9 Hz, 1H), 4.83 (s, 46H), 4.52 - 4.25 (m, 3H), 4.16 (d, J = 13.4 Hz, 2H), 3.96 (d, J = 13.1 Hz, 1H), 3.67 (d, J = 15.7 Hz, 7H), 3.26 (s, 5H), 2.97 - 2.72 (m, 4H), 2.02 (s, 2H), 1.28 - 1.08 (m, 10H), 1.02 (s, 3H).

**EXAMPLE 98**

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(4-fluoropyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-

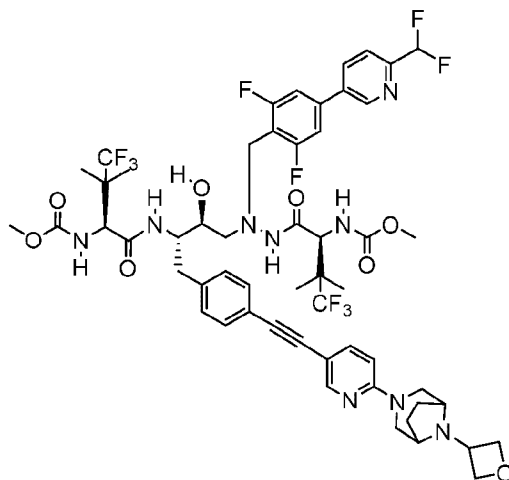
- 5 **yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (98). Intermediates: **I2**, **P15**, and **S48**. MS (ESI) m/z 1109.1 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.66 (dd, J = 8.6, 5.6 Hz, 1H), 8.34 - 8.27 (m, 1H), 8.16 (d, J = 9.3 Hz, 1H), 7.86 (t, J = 8.4 Hz, 1H), 7.80 - 7.61 (m, 4H), 7.61 - 7.48 (m, 1H), 7.33 (d, J = 7.9 Hz, 2H), 7.28 - 7.17 (m, 3H), 7.14 (d, J = 9.8 Hz, 1H), 6.99 - 6.92 (m, 1H),**
- 10 6.79 (d, J = 10.0 Hz, 1H), 4.86 (s, 32H), 4.54 - 4.39 (m, 2H), 4.35 - 4.26 (m, 1H), 4.17 (d, J = 13.1 Hz, 2H), 3.95 (t, J = 17.4 Hz, 4H), 3.67 (d, J = 16.6 Hz, 7H), 2.98 - 2.73 (m, 4H), 1.28 (d, J = 13.9 Hz, 5H), 1.20 - 1.08 (m, 10H), 1.03 (s, 3H).



EXAMPLE 99

Methyl ((5S,8S,9S,14S)-11-(4-(5-(difluoromethyl)pyridin-2-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (99).

Intermediates: **I2**, **P35**, and **S3**. MS (ESI) m/z 1167.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.15 (d, $J = 9.4$ Hz, 1H), 8.10 – 8.00 (m, 3H), 7.72 – 7.60 (m, 4H), 7.33 (d, $J = 7.9$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 7.11 (d, $J = 18.4$ Hz, 1H), 6.88 – 6.75 (m, 3H), 4.96 (t, $J = 7.6$ Hz, 2H), 4.80 (d, $J = 5.0$ Hz, 1H), 4.54 (s, 1H), 4.47 – 4.42 (m, 1H), 4.33 (dd, $J = 16.8, 11.9$ Hz, 4H), 4.20 – 4.12 (m, 4H), 3.98 (d, $J = 13.1$ Hz, 1H), 3.67 (d, $J = 17.6$ Hz, 8H), 3.39 (d, $J = 13.7$ Hz, 2H), 2.90 (dd, $J = 10.5, 7.0$ Hz, 3H), 2.84 – 2.77 (m, 1H), 2.27 – 2.19 (m, 2H), 2.11 – 2.04 (m, 2H), 1.18 – 1.11 (m, 9H), 1.03 (s, 3H).



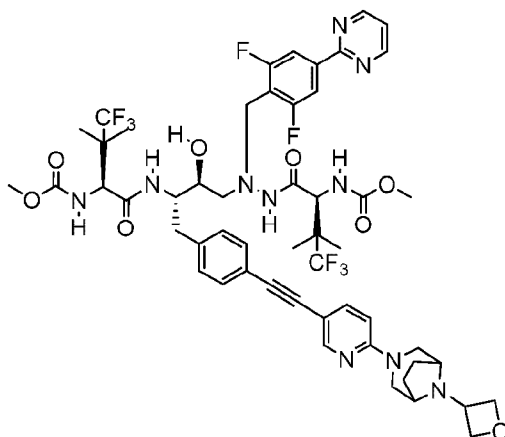
15

EXAMPLE 100

Methyl ((5S,8S,9S,14S)-11-(4-(6-(difluoromethyl)pyridin-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (100).

Intermediates: **I2**, **P45**, and **S3**. MS (ESI) m/z 1165.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.91 (d, $J = 1.8$ Hz, 1H), 8.31 – 8.22 (m, 2H), 7.79 (d, $J = 8.2$ Hz, 1H), 7.73 – 7.61 (m, 2H), 7.34 (dd, $J = 8.2, 3.3$ Hz, 4H), 7.25 – 7.15 (m, 3H), 6.93 – 6.84 (m, 2H), 6.77 (s, 1H), 4.96 (t, $J = 7.6$ Hz, 2H), 4.82 – 4.79 (m, 2H), 4.54 (s, 1H), 4.38 – 4.28 (m, 4H), 4.16 (s, 4H), 3.98 (d,

$J = 13.2$ Hz, 1H), 3.67 (d, $J = 21.9$ Hz, 7H), 3.39 (d, $J = 13.8$ Hz, 2H), 2.96 – 2.76 (m, 5H), 2.28 – 2.20 (m, 2H), 2.12 – 2.04 (m, 2H), 1.23 – 1.12 (m, 9H), 1.04 (s, 3H).

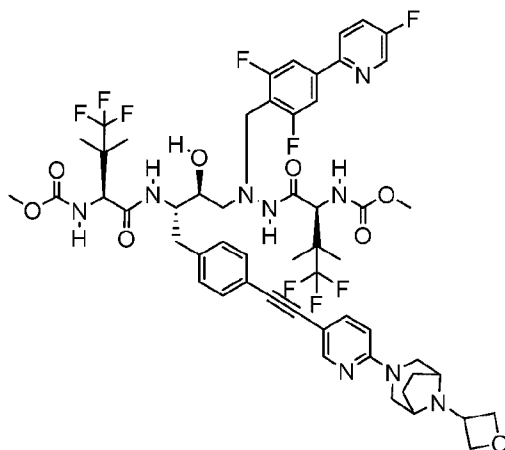


5

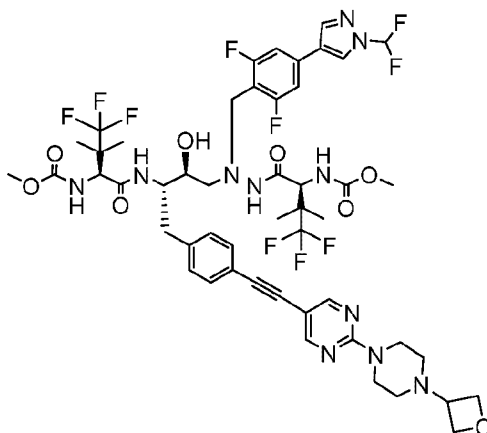
EXAMPLE 101

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyrimidin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (101). Intermediates: **I2**, **P16**, and **S3**. MS (ESI) m/z 1116.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.87 (dd, $J = 4.9, 4.1$ Hz, 2H), 8.32 – 8.27 (m, 1H), 8.15 (d, $J = 9.3$ Hz, 1H), 7.97 (d, $J = 8.5$ Hz, 2H), 7.70 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.44 – 7.29 (m, 4H), 7.24 (t, $J = 9.4$ Hz, 2H), 7.07 (t, $J = 13.8$ Hz, 1H), 6.81 (dd, $J = 34.9, 9.4$ Hz, 2H), 4.96 (t, $J = 7.6$ Hz, 2H), 4.82 – 4.78 (m, 2H), 4.61 – 4.41 (m, 3H), 4.33 (dd, $J = 18.6, 12.0$ Hz, 4H), 4.16 (s, 4H), 3.99 (d, $J = 13.1$ Hz, 1H), 3.68 (d, $J = 8.8$ Hz, 6H), 3.41 – 3.35 (m, 2H), 2.95 – 2.76 (m, 4H), 2.27 – 2.20 (m, 2H), 2.08 (d, $J = 8.7$ Hz, 2H), 1.15 (dd, $J = 14.6, 11.3$ Hz, 9H), 1.03 (s, 3H).

15

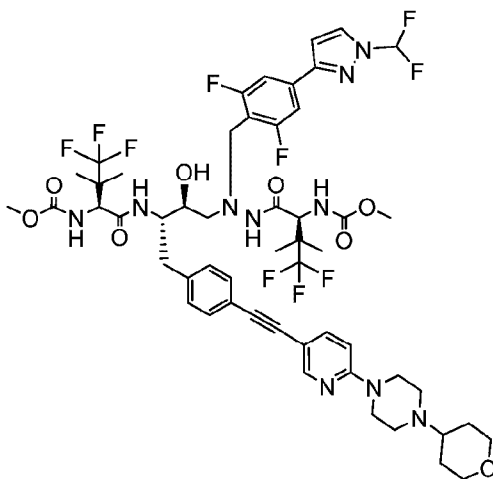
**EXAMPLE 102**

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(5-fluoropyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (102). Intermediates: **I2**, **P14**, and **S3**. MS (ESI) m/z 1135.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.54 (d, J = 2.9 Hz, 1H), 7.97 – 7.94 (m, 1H), 7.70 – 7.53 (m, 12H), 7.33 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.9 Hz, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.84 – 4.81 (m, 1H), 4.54 (s, 1H), 4.44 (t, J = 5.0 Hz, 1H), 4.38 – 4.29 (m, 3H), 4.15 (d, J = 5.9 Hz, 4H), 3.98 (s, 1H), 3.67 (d, J = 15.3 Hz, 8H), 3.44 – 3.37 (m, 2H), 2.92 – 2.74 (m, 4H), 2.23 (dd, J = 9.6, 4.5 Hz, 2H), 2.12 – 2.03 (m, 2H), 1.18 – 1.10 (m, 8H), 1.03 (s, 3H).

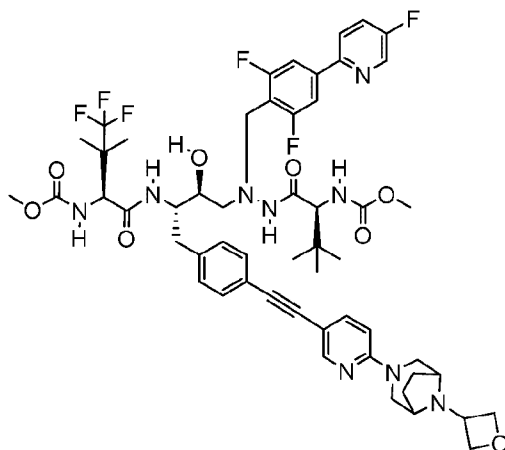


EXAMPLE 103

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-(4-(oxetan-3-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (103). Intermediates: **I2**, **P7**, and **S49**. MS (ESI) m/z 1130.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.53 (d, $J = 4.0$ Hz, 3H), 8.19 – 8.11 (m, 3H), 7.38 – 7.32 (m, 3H), 7.24 (t, $J = 8.0$ Hz, 5H), 7.16 (d, $J = 9.9$ Hz, 1H), 4.90 (t, $J = 7.6$ Hz, 3H), 4.83 – 4.78 (m, 1H), 4.48 – 4.36 (m, 3H), 4.31 (d, $J = 10.0$ Hz, 1H), 4.17 – 4.08 (m, 4H), 3.93 (d, $J = 13.3$ Hz, 1H), 3.67 (d, $J = 9.7$ Hz, 9H), 2.93 – 2.72 (m, 6H), 1.19 – 1.09 (m, 11H), 1.03 (s, 3H).

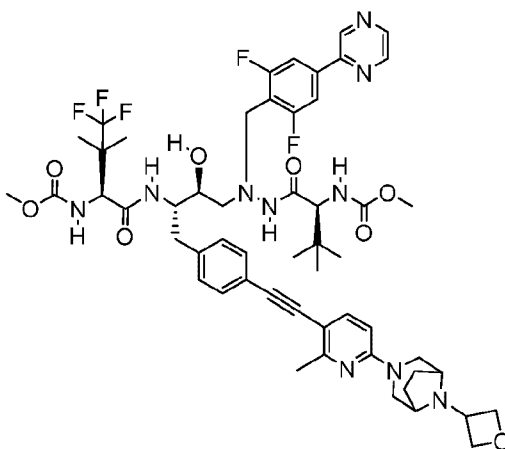
**EXAMPLE 104**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-((6-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (104). Intermediates: **I2**, **P4**, and **S50**. MS (ESI) m/z 1158.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.31 – 8.29 (m, 1H), 8.16 (d, $J = 9.4$ Hz, 1H), 8.10 (d, $J = 2.7$ Hz, 1H), 7.73 – 7.61 (m, 2H), 7.45 (d, $J = 8.3$ Hz, 3H), 7.33 (d, $J = 7.8$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 3H), 6.94 (dd, $J = 5.7, 3.0$ Hz, 2H), 4.30 (d, $J = 9.9$ Hz, 1H), 4.19 – 4.06 (m, 5H), 3.95 (d, $J = 13.2$ Hz, 1H), 3.68 (d, $J = 11.0$ Hz, 10H), 3.47 (ddd, $J = 24.1, 12.1, 9.2$ Hz, 5H), 2.93 – 2.74 (m, 5H), 2.11 (d, $J = 10.4$ Hz, 3H), 1.77 (qd, $J = 12.1, 4.6$ Hz, 3H), 1.18 – 1.10 (m, 10H), 1.03 (s, 3H).

**EXAMPLE 105**

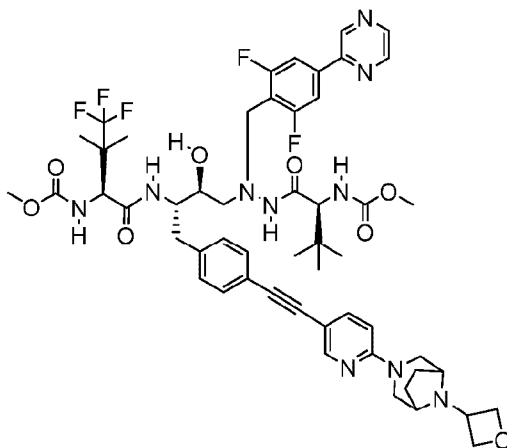
Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(5-fluoropyridin-2-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (105). Intermediates: **I3**, **P14**, and **S3**. MS (ESI) m/z 1081.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.54 (d, $J = 2.9$ Hz, 1H), 8.29 (d, $J = 2.2$ Hz, 1H), 8.15 (d, $J = 9.4$ Hz, 1H), 7.95 (dd, $J = 8.9, 4.2$ Hz, 1H), 7.76 – 7.64 (m, 2H), 7.60 (d, $J = 8.7$ Hz, 2H), 7.32 (d, $J = 7.9$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 2H), 6.94 – 6.80 (m, 1H), 4.96 (t, $J = 7.6$ Hz, 2H), 4.85 (s, 14H), 4.54 (s, 1H), 4.43 (s, 1H), 4.39 – 4.28 (m, 2H), 4.18 – 4.09 (m, 4H), 3.99 (d, $J = 13.0$ Hz, 1H), 3.82 – 3.58 (m, 8H), 3.41 – 3.33 (m, 2H), 3.00 – 2.71 (m, 4H), 2.23 (dd, $J = 9.8, 4.6$ Hz, 2H), 2.14 – 2.01 (m, 2H), 1.13 (d, $J = 12.5$ Hz, 6H), 0.86 (s, 9H).

15



EXAMPLE 106

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(5-fluoropyridin-2-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (106). Intermediates: **I3**, **P36**, and **S45**. MS (ESI) m/z 1078.8 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.71 (s, 1H), 8.16 (d, $J = 9.4$ Hz, 1H), 7.72 (d, $J = 8.3$ Hz, 2H), 7.62 (d, $J = 8.7$ Hz, 1H), 7.32 (d, $J = 7.8$ Hz, 2H), 7.24 (s, 0H), 6.81 (d, $J = 9.9$ Hz, 1H), 6.67 (d, $J = 8.7$ Hz, 1H), 4.96 (t, $J = 7.6$ Hz, 2H), 4.54 (s, 1H), 4.50 – 4.30 (m, 3H), 4.15 (t, $J = 10.1$ Hz, 4H), 4.01 (d, $J = 13.1$ Hz, 1H), 3.81 – 3.55 (m, 7H), 3.37 (d, $J = 13.8$ Hz, 2H), 3.00 – 2.74 (m, 4H), 2.56 (s, 3H), 2.22 (dd, $J = 9.6, 4.4$ Hz, 2H), 2.13 – 1.97 (m, 2H), 1.14 (d, $J = 10.5$ Hz, 6H), 0.85 (s, 9H).

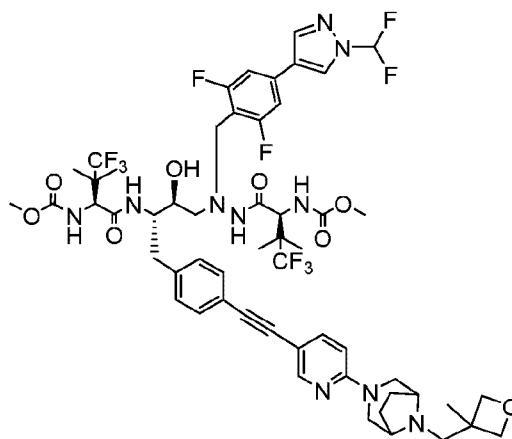


15

EXAMPLE 107

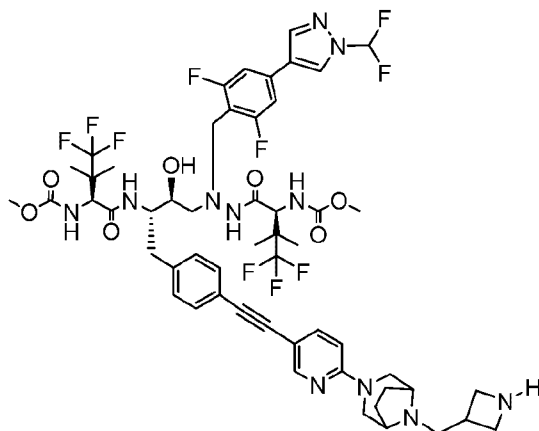
Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyrazin-2-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (107). Intermediates: **I3**, **P36**, and **S3**. MS (ESI) m/z 1064.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 9.15 (s, 1H), 8.59 (s, 1H), 8.32 – 8.26 (m, 1H), 7.76 – 7.66 (m, 3H), 7.33 (d, $J = 7.8$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 6.89 – 6.84 (m, 1H), 6.79 (d, $J = 9.8$ Hz, 1H), 4.96 (t, $J = 7.6$ Hz, 3H), 4.84 – 4.79 (m, 3H), 4.54 (s, 1H), 4.44 (d, $J = 6.5$ Hz, 1H), 4.39 – 4.31 (m, 2H), 4.16 (d, $J = 4.9$ Hz, 4H), 4.01 (d, $J = 13.1$ Hz, 1H), 3.78 – 3.63 (m, 9H), 3.43 – 3.36 (m, 2H), 2.94 – 2.77 (m, 5H), 2.27 – 2.19 (m, 2H), 2.11 – 2.04 (m, 2H), 1.13 (d, $J = 10.7$

Hz, 6H), 0.86 (s, 9H).



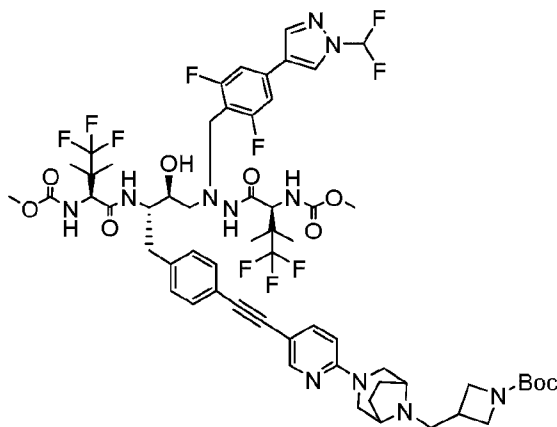
EXAMPLE 108

- 5 **Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-((3-methyloxetan-3-yl)methyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (108).**
- Intermediates: **I2**, **P7**, and **S56**. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.52 (d, *J* = 0.7 Hz, 1H),
 10 8.28 (d, *J* = 2.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 2H), 7.75 – 7.61 (m, 2H), 7.57 – 7.46 (m, 1H), 7.39 – 7.30 (m, 2H), 7.23 (dd, *J* = 10.8, 8.2 Hz, 4H), 7.12 (d, *J* = 9.9 Hz, 1H), 6.80 (dd, *J* = 31.1, 9.4 Hz, 2H), 4.61 (d, *J* = 6.3 Hz, 2H), 4.50 – 4.36 (m, 3H), 4.30 – 4.23 (m, 3H), 4.12 (d, *J* = 12.2 Hz, 3H), 3.93 (d, *J* = 13.2 Hz, 1H), 3.81 (d, *J* = 11.0 Hz, 0H), 3.68 (d, *J* = 10.0 Hz, 6H), 3.56 (s, 1H), 3.45 (d, *J* = 14.1 Hz, 1H), 2.98 – 2.64 (m, 4H), 2.38 (d, *J* = 11.2 Hz, 2H), 2.19 – 2.05 (m,
 15 2H), 1.62 (s, 2H), 1.22 – 1.08 (m, 9H), 1.00 (d, *J* = 26.6 Hz, 4H).

**EXAMPLE 109**

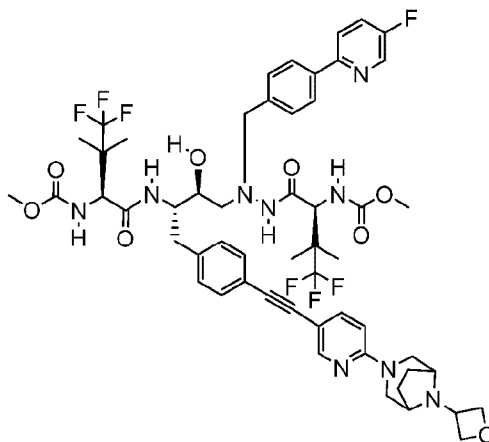
Methyl ((5S,8S,9S,14S)-8-(4-((6-(8-(azetidin-3-ylmethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (109)

Intermediates: **I2**, **P7**, and **S51** followed by treatment with trifluoroacetic acid to remove the Boc-group. MS (ESI) m/z 1169.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.51 (d, J = 0.7 Hz, 1H), 8.11 (s, 2H), 7.70 (dd, J = 8.9, 2.3 Hz, 1H), 7.35 – 7.31 (m, 2H), 7.26 – 7.20 (m, 4H), 6.87 – 6.84 (m, 1H), 4.44 (d, J = 6.5 Hz, 1H), 4.33 – 4.22 (m, 6H), 4.19 – 4.04 (m, 7H), 3.93 (d, J = 13.2 Hz, 1H), 3.68 (d, J = 9.4 Hz, 9H), 3.54 (s, 3H), 3.43 (d, J = 13.7 Hz, 3H), 2.93 – 2.73 (m, 5H), 2.28 (dd, J = 8.6, 3.7 Hz, 2H), 2.13 – 2.05 (m, 2H), 1.19 – 1.10 (m, 9H), 1.04 (s, 3H).



EXAMPLE 110

tert-butyl 3-((3-(5-((4-((2S,3S)-4-(1-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-2-((S)-4,4,4-trifluoro-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)hydrazinyl)-3-hydroxy-2-((S)-4,4,4-trifluoro-2-((methoxycarbonyl)amino)-3,3-dimethylbutanamido)butyl)phenyl)ethynyl)pyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methyl)azetidine-1-carboxylate (110). Intermediates: **I2**, **P7**, and **S51**. MS (ESI) m/z 1268.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.51 (d, $J = 0.7$ Hz, 1H), 8.11 (s, 2H), 7.70 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.35 – 7.31 (m, 2H), 7.26 – 7.19 (m, 4H), 6.88 – 6.84 (m, 1H), 4.44 (d, $J = 6.5$ Hz, 1H), 4.33 – 4.22 (m, 6H), 4.19 – 4.05 (m, 7H), 3.93 (d, $J = 13.2$ Hz, 2H), 3.68 (d, $J = 9.4$ Hz, 16H), 3.54 (s, 3H), 3.43 (d, $J = 13.7$ Hz, 2H), 2.94 – 2.74 (m, 6H), 2.28 (dd, $J = 8.6, 3.7$ Hz, 2H), 2.12 – 2.06 (m, 2H), 1.18 – 1.10 (m, 9H), 1.04 (s, 3H).

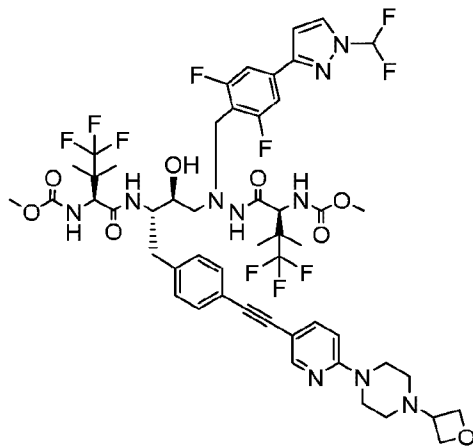


15

EXAMPLE 111

Methyl ((5S,8S,9S,14S)-16,16,16-trifluoro-11-(4-(5-fluoropyridin-2-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (111). Intermediates: **I2**, **P37**, and **S3**. MS (ESI) m/z 1100.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.50 (d, $J = 2.9$ Hz, 1H), 7.88 (dd, $J = 8.7, 4.2$ Hz, 3H), 7.72 – 7.63 (m, 3H), 7.49 (d, $J = 7.9$ Hz, 2H), 7.33 (d, $J = 7.8$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 1H), 4.96 (t, $J = 7.6$ Hz, 2H), 4.84 – 4.80 (m, 3H), 4.54 (s, 1H), 4.42 – 4.32 (m, 4H), 4.25 (d, $J = 6.6$ Hz, 1H), 4.15 (d, $J = 4.7$ Hz, 3H), 4.05 – 4.00 (m, 1H), 3.92 (d, $J = 13.3$ Hz, 1H), 3.75 (d, $J = 8.3$ Hz, 1H), 3.68 (s, 3H), 3.58 (s, 3H), 3.39 (d, $J = 13.8$ Hz,

3H), 2.93 – 2.71 (m, 5H), 2.28 – 2.19 (m, 2H), 2.07 (d, $J = 8.6$ Hz, 2H), 1.11 (d, $J = 8.0$ Hz, 7H), 1.02 (s, 3H), 0.83 (s, 3H).

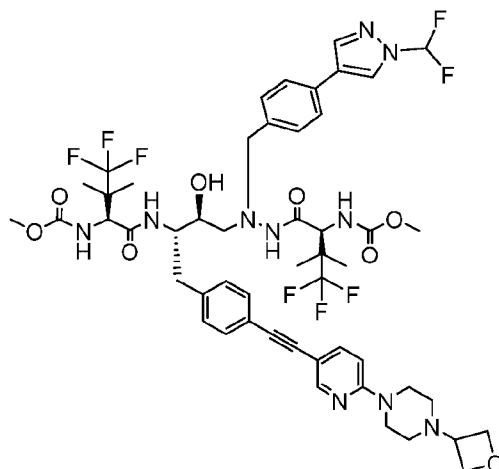


5

EXAMPLE 112

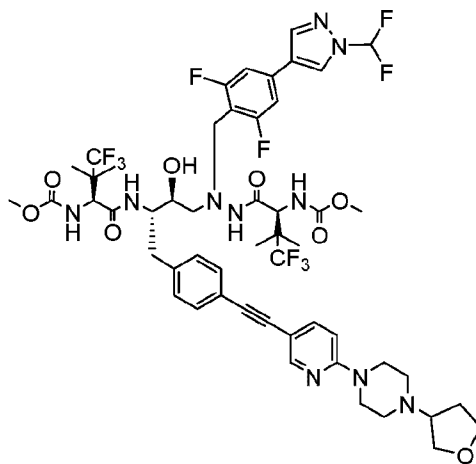
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (112). Intermediates: **12**, **P4**, and **S48**. MS

(ESI) m/z 1129.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.33 – 8.29 (m, 1H), 8.14 (d, $J = 9.4$ Hz, 1H), 8.10 (d, $J = 2.7$ Hz, 1H), 7.74 – 7.61 (m, 2H), 7.53 (s, 1H), 7.45 (t, $J = 6.9$ Hz, 2H), 7.39 – 7.31 (m, 3H), 7.22 (d, $J = 8.2$ Hz, 3H), 7.09 (d, $J = 9.9$ Hz, 1H), 6.98 – 6.91 (m, 2H), 4.94 – 4.88 (m, 3H), 4.42 (td, $J = 7.9, 7.2, 4.1$ Hz, 2H), 4.35 – 4.27 (m, 2H), 4.20 – 4.11 (m, 3H), 3.95 (d, $J = 13.2$ Hz, 3H), 3.79 – 3.65 (m, 11H), 2.94 – 2.84 (m, 3H), 2.83 – 2.74 (m, 1H), 1.21 – 1.10 (m, 9H), 1.04 (d, $J = 7.2$ Hz, 3H).



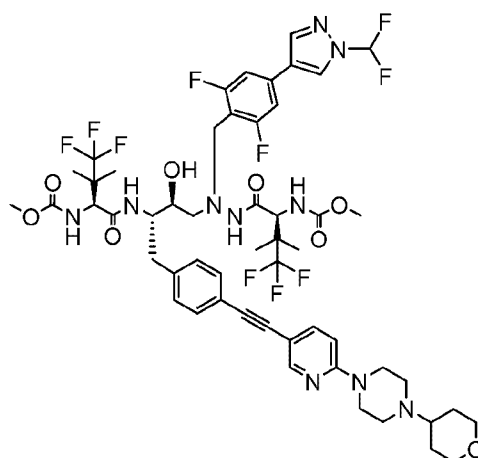
EXAMPLE 113

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (113). Intermediates: **I2**, **P9**, and **S48**. MS (ESI) m/z 1093.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.38 (s, 1H), 8.31 – 8.28 (m, 1H), 8.06 (s, 1H), 7.70 (dd, J = 8.8, 2.3 Hz, 1H), 7.57 – 7.52 (m, 3H), 7.48 (s, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 7.4 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 8.9 Hz, 1H), 4.94 – 4.89 (m, 3H), 4.85 – 4.80 (m, 2H), 4.45 – 4.37 (m, 3H), 4.25 (s, 1H), 4.15 (s, 1H), 4.01 – 3.84 (m, 6H), 3.74 (d, J = 8.9 Hz, 1H), 3.68 (s, 3H), 3.60 (s, 3H), 2.89 (d, J = 8.9 Hz, 2H), 2.85 – 2.67 (m, 3H), 1.28 (d, J = 13.9 Hz, 5H), 1.11 (d, J = 12.5 Hz, 6H), 1.01 (s, 3H), 0.88 – 0.81 (m, 3H).

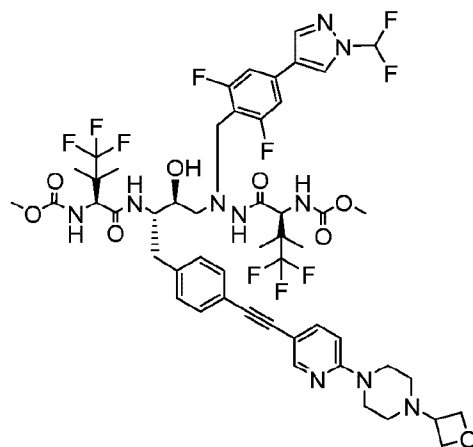


EXAMPLE 114

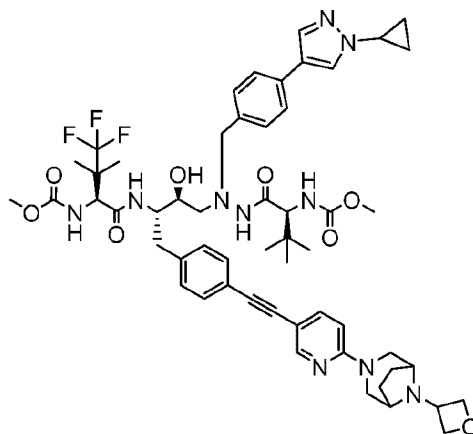
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-(((6-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (114). Intermediates: **I2**, **P7**, and **S57**. MS (ESI) m/z 1144.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 1H), 8.30 (d, $J = 2.2$ Hz, 1H), 8.12 (s, 2H), 7.71 – 7.64 (m, 1H), 7.36 – 7.30 (m, 2H), 7.23 (dd, $J = 11.8, 8.2$ Hz, 4H), 7.13 (d, $J = 9.8$ Hz, 1H), 6.93 (d, $J = 8.9$ Hz, 1H), 6.78 (d, $J = 9.9$ Hz, 1H), 4.46 – 4.41 (m, 1H), 4.31 (d, $J = 9.5$ Hz, 1H), 4.21 – 4.00 (m, 7H), 3.97 – 3.85 (m, 3H), 3.78 – 3.65 (m, 9H), 3.42 (s, 5H), 2.94 – 2.74 (m, 5H), 2.43 (dtd, $J = 12.8, 8.2, 4.3$ Hz, 2H), 2.24 (ddd, $J = 13.7, 9.2, 5.0$ Hz, 1H), 1.20 – 1.10 (m, 9H), 1.03 (s, 3H).

**EXAMPLE 115**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-(((6-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (115). Intermediates: **I2**, **P7**, and **S50**. MS (ESI) m/z 1158.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.52 (d, $J = 0.8$ Hz, 1H), 8.30 (dd, $J = 2.3, 0.8$ Hz, 1H), 8.12 (d, $J = 6.0$ Hz, 2H), 7.70 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.36 – 7.31 (m, 3H), 7.27 – 7.20 (m, 5H), 6.96 – 6.91 (m, 1H), 4.43 (d, $J = 9.7$ Hz, 2H), 4.31 (d, $J = 9.9$ Hz, 1H), 4.11 (dq, $J = 11.3, 6.3, 4.7$ Hz, 5H), 3.93 (d, $J = 13.2$ Hz, 2H), 3.68 (d, $J = 10.2$ Hz, 9H), 3.56 – 3.40 (m, 5H), 2.93 – 2.73 (m, 5H), 2.14 – 2.06 (m, 3H), 1.77 (qd, $J = 12.1, 4.7$ Hz, 3H), 1.18 – 1.11 (m, 10H), 1.03 (s, 3H).

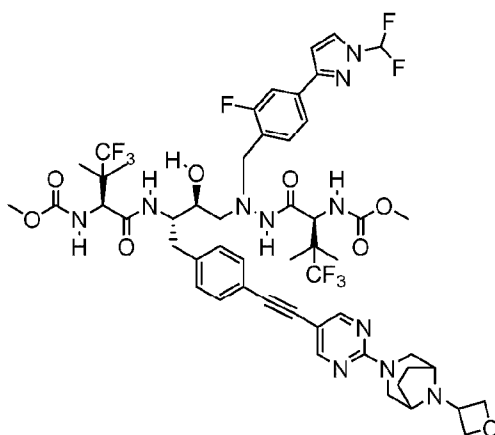
**EXAMPLE 116**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(((6-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (116). Intermediates: **I2**, **P7**, and **S48**. MS (ESI) m/z 1130.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.53 (d, $J = 0.7$ Hz, 1H), 8.31 – 8.28 (m, 1H), 8.13 (d, $J = 10.9$ Hz, 2H), 7.70 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.36 – 7.30 (m, 3H), 7.23 (dd, $J = 11.5, 8.1$ Hz, 5H), 7.13 (d, $J = 10.0$ Hz, 1H), 6.95 (d, $J = 8.8$ Hz, 1H), 4.90 (t, $J = 7.7$ Hz, 3H), 4.82 (s, 2H), 4.42 (ddd, $J = 9.9, 7.1, 3.6$ Hz, 2H), 4.31 (d, $J = 10.0$ Hz, 1H), 4.20 – 4.09 (m, 3H), 3.93 (d, $J = 11.8$ Hz, 5H), 3.68 (d, $J = 10.1$ Hz, 8H), 2.95 – 2.73 (m, 5H), 1.21 – 1.10 (m, 10H), 1.03 (s, 4H).



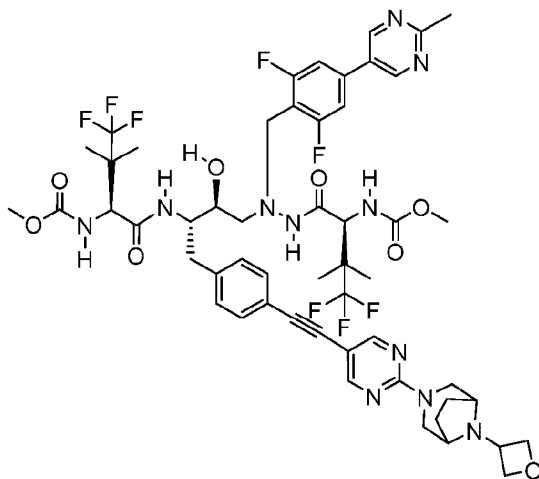
EXAMPLE 117

Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-4-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (117). Intermediates: **I3**, **P46**, and **S3**. MS (ESI) m/z 1056.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 7.99 (s, 1H), 7.77 (s, 1H), 7.70 (dd, J = 8.9, 2.3 Hz, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.39 – 7.30 (m, 5H), 7.20 (d, J = 8.1 Hz, 2H), 6.86 (d, J = 8.9 Hz, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.82 (dd, J = 8.2, 5.1 Hz, 3H), 4.54 (s, 1H), 4.41 – 4.31 (m, 4H), 4.18 – 4.09 (m, 3H), 3.97 – 3.87 (m, 2H), 3.77 (d, J = 9.6 Hz, 1H), 3.73 – 3.60 (m, 9H), 3.44 – 3.36 (m, 2H), 2.96 – 2.75 (m, 4H), 2.26 – 2.19 (m, 2H), 2.10 – 2.04 (m, 2H), 1.15 – 0.97 (m, 11H), 0.77 (s, 9H).

**EXAMPLE 118**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-fluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (118). Intermediates: **I2**, **P5**, and **S7**. MS (ESI) m/z 1138.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.52 (d, J = 1.0 Hz, 2H), 8.10 (d, J = 9.4 Hz, 1H), 7.76 (d, J = 1.7 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.45 (t, J = 58.0 Hz, 1H), 7.34 (d, J = 7.9 Hz, 2H), 7.26 - 7.18 (m, 4H), 7.16 (d, J = 9.8 Hz, 1H), 6.79 (d, J = 9.9 Hz, 1H), 6.56 (d, J = 1.7 Hz, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.76 (s, 1H), 4.48 - 4.36 (m, 1H), 4.28 - 4.18 (m, 2H), 4.14 (s, 3H), 4.08 (s, 1H), 3.98 (d, J = 13.7 Hz, 1H), 3.75 (s, 1H), 3.58 (s, 3H), 3.47 (d, J = 14.5 Hz, 2H), 2.91 (d, J = 9.2 Hz, 2H), 2.83 (d, J = 6.6 Hz,

2H), 2.27 - 2.15 (m, 2H), 1.99 (d, J = 8.8 Hz, 2H), 1.14 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 0.95 (s, 3H).

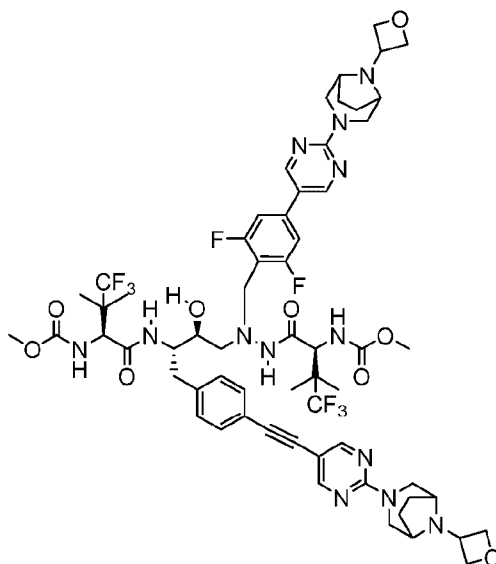


5

EXAMPLE 119

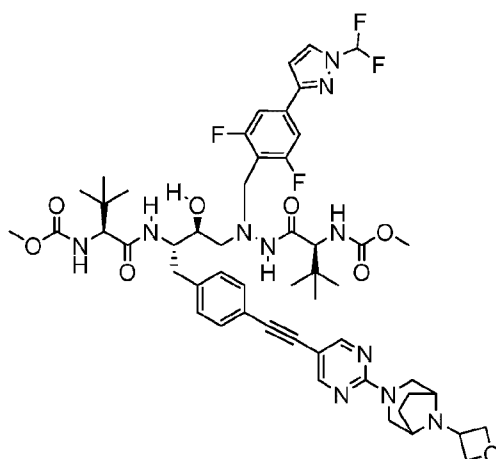
Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(2-methylpyrimidin-5-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (119). Intermediates: 12, P47, and S7.

- 10 MS (ESI) m/z 1133.32 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.97 (s, 1H), 8.52 (s, 1H), 8.14 (d, J = 9.4 Hz, 1H), 7.34 (dd, J = 8.0, 5.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 10.0 Hz, 2H), 6.79 (d, J = 9.9 Hz, 2H), 4.96 (t, J = 7.6 Hz, 2H), 4.81 - 4.73 (m, 6H), 4.44 (d, J = 9.9 Hz, 2H), 4.29 (d, J = 10.0 Hz, 2H), 4.16 (d, J = 14.0 Hz, 2H), 3.96 (d, J = 13.2 Hz, 1H), 3.67 (d, J = 15.8 Hz, 10H), 3.46 (d, J = 14.5 Hz, 1H), 3.20 - 3.12 (m, 2H), 2.95 - 2.79 (m, 2H), 2.74 (s, 3H), 2.22 (dd, J = 14.5, 8.2 Hz, 1H), 1.99 (d, J = 8.8 Hz, 1H), 1.27 - 1.09 (m, 10H), 1.04 (s, 6H).
- 15

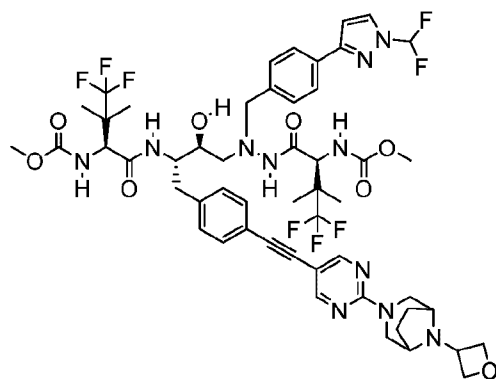


EXAMPLE 120

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (120). Intermediates: **I2**, **P20**, and **S7**. MS (ESI) m/z 1284.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.73 (s, 2H), 8.53 (s, 2H), 8.19 (d, J = 9.4 Hz, 1H), 7.35 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 8.5 Hz, 5H), 6.84 (d, J = 9.8 Hz, 1H), 5.04 - 4.92 (m, 5H), 4.80 (d, J = 4.3 Hz, 2H), 4.44 (d, J = 9.9 Hz, 1H), 4.31 (d, J = 10.0 Hz, 1H), 4.15 (s, 6H), 3.95 (d, J = 13.2 Hz, 1H), 3.74 (s, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.47 (dd, J = 14.4, 9.6 Hz, 5H), 2.91 (d, J = 7.7 Hz, 2H), 2.79 (d, J = 9.6 Hz, 1H), 2.21 (s, 4H), 1.99 (t, J = 7.3 Hz, 5H), 1.17 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H).

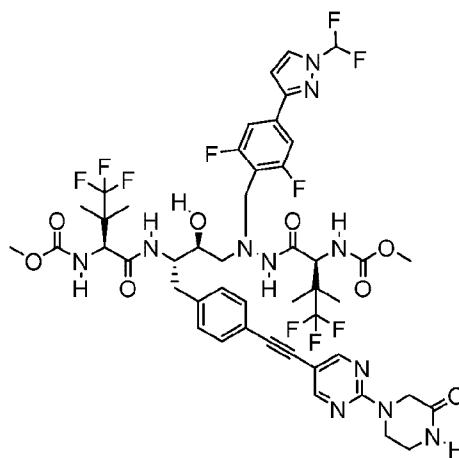
**EXAMPLE 121**

Methyl ((5S,8S,9S,14S)-5-(tert-butyl)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (121). Intermediates: **I1**, **P4**, and **S7**. MS (ESI) m/z 1048.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.44 (s, 2H), 8.01 (d, $J = 2.7$ Hz, 1H), 7.77 (d, $J = 9.5$ Hz, 1H), 7.44 (t, $J = 59.7$ Hz, 1H), 7.35 (d, $J = 8.2$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.15 (d, $J = 8.0$ Hz, 2H), 6.84 (d, $J = 2.8$ Hz, 1H), 4.87 (dd, $J = 8.1, 7.0$ Hz, 2H), 4.71 (dd, $J = 8.1, 5.1$ Hz, 2H), 4.02 (d, $J = 13.8$ Hz, 4H), 3.87 (d, $J = 13.4$ Hz, 1H), 3.80 (s, 1H), 3.72 - 3.62 (m, 1H), 3.58 (s, 3H), 3.55 (s, 2H), 3.38 (d, $J = 1.6$ Hz, 1H), 3.34 (s, 1H), 2.83 (t, $J = 7.0$ Hz, 1H), 2.72 (s, 2H), 2.11 (s, 2H), 1.89 (d, $J = 9.1$ Hz, 2H), 0.79 (s, 8H), 0.74 (s, 8H).

**EXAMPLE 122**

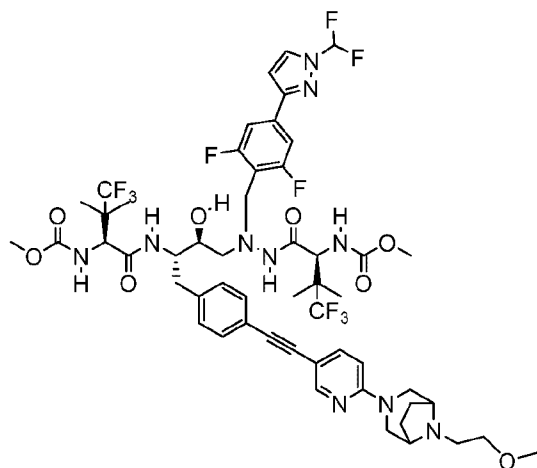
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (122).

trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (**122**). Intermediates: **I2**, **P6**, and **S7**. MS (ESI) m/z 1121.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 2H), 8.09 (d, $J = 9.4$ Hz, 1H), 8.04 (d, $J = 2.7$ Hz, 1H), 7.78 (d, $J = 8.1$ Hz, 2H), 7.49 (t, $J = 60.0$ Hz, 1H), 7.44 (d, $J = 8.1$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 9.8$ Hz, 1H), 6.86 (d, $J = 2.7$ Hz, 1H), 6.76 (d, $J = 9.9$ Hz, 1H), 4.95 (t, $J = 7.6$ Hz, 2H), 4.82 - 4.78 (m, 2H), 4.75 (s, 1H), 4.39 (d, $J = 9.8$ Hz, 1H), 4.24 (d, $J = 9.8$ Hz, 1H), 4.18 (d, $J = 8.3$ Hz, 1H), 4.16 - 4.08 (m, 2H), 4.00 (d, $J = 13.1$ Hz, 1H), 3.88 (d, $J = 13.4$ Hz, 1H), 3.74 (s, 1H), 3.67 (s, 3H), 3.59 (s, 3H), 3.46 (d, $J = 14.5$ Hz, 2H), 2.96 - 2.86 (m, 2H), 2.86 - 2.68 (m, 2H), 2.29 - 2.13 (m, 2H), 2.04 - 1.88 (m, 2H), 1.11 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H), 0.84 (s, 3H).



EXAMPLE 123

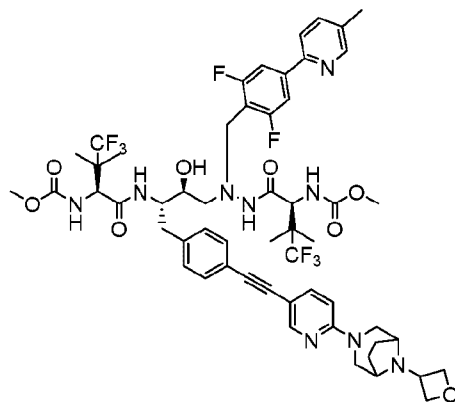
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-(4-((2-(3-oxopiperazin-1-yl)pyrimidin-5-yl)ethynyl)benzyl)-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (**123**). Intermediates: **I2**, **P4**, and **S58a**. MS (ESI) m/z 1088.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.49 (s, 2H), 7.53 (t, $J = 59.7$ Hz, 1H), 7.45 (d, $J = 8.2$ Hz, 2H), 7.34 (d, $J = 7.8$ Hz, 2H), 7.23 (d, $J = 8.1$ Hz, 2H), 7.14 (d, $J = 10.1$ Hz, 1H), 6.94 (d, $J = 2.8$ Hz, 1H), 6.82 (d, $J = 10.0$ Hz, 1H), 4.50 - 4.39 (m, 1H), 4.38 (s, 2H), 4.34 - 4.26 (m, 1H), 4.14 (d, $J = 12.5$ Hz, 2H), 4.10 - 3.99 (m, 2H), 3.94 (d, $J = 13.1$ Hz, 1H), 3.80 - 3.72 (m, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 3.45 - 3.38 (m, 2H), 2.94 - 2.82 (m, 3H), 2.82 - 2.73 (m, 1H), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.06 - 0.99 (m, 3H).

**EXAMPLE 124**

- 5 **Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-8-(((6-(8-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (124).**

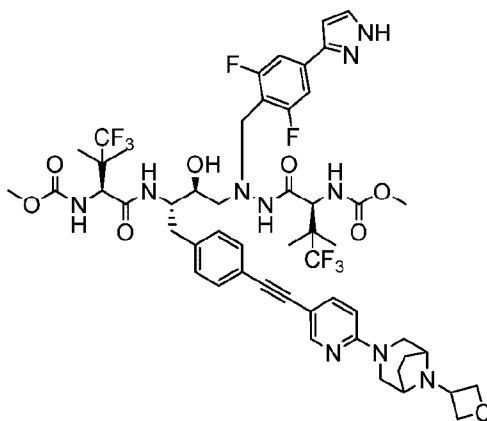
Intermediates: **I2**, **P4**, and **S59**. MS (ESI) m/z 1157.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol-
 10 d_4) δ 8.28 (d, $J = 2.2$ Hz, 1H), 8.20 – 8.07 (m, 1H), 7.74 – 7.66 (m, 1H), 7.48 – 7.30 (m, 4H),
 7.22 (d, $J = 8.0$ Hz, 2H), 6.93 (d, $J = 2.8$ Hz, 1H), 6.86 (d, $J = 8.9$ Hz, 1H), 4.44 (s, 1H), 4.31 (s,
 1H), 4.28 (s, 3H), 4.14 (d, $J = 12.1$ Hz, 2H), 3.94 (d, $J = 13.1$ Hz, 1H), 3.83 – 3.77 (m, 2H), 3.68
 (d, $J = 12.0$ Hz, 7H), 3.44 (s, 4H), 3.35 (s, 3H), 2.94 – 2.84 (m, 3H), 2.78 (dd, $J = 12.6, 9.1$ Hz,
 1H), 2.32 – 2.24 (m, 2H), 2.06 (d, $J = 8.6$ Hz, 2H), 1.24 – 1.09 (m, 8H), 1.03 (s, 2H).

15



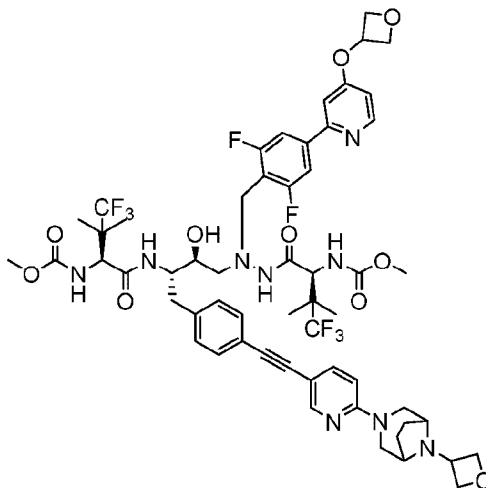
EXAMPLE 125

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(5-methylpyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (125). Intermediates: **I2**, **P39**, and **S3**. MS (ESI) m/z 1128.8 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.56 (s, 1H), 8.29 (d, $J = 2.2$ Hz, 1H), 8.14 (d, $J = 9.5$ Hz, 1H), 8.01 – 7.88 (m, 2H), 7.70 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.33 (d, $J = 7.9$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 6.83 (dd, $J = 28.9, 9.4$ Hz, 2H), 4.96 (t, $J = 7.6$ Hz, 2H), 4.48 – 4.40 (m, 1H), 4.39 – 4.27 (m, 3H), 4.22 – 4.12 (m, 4H), 3.98 (d, $J = 13.1$ Hz, 1H), 3.75 (s, 1H), 3.70 (s, 3H), 3.64 (s, 3H), 3.46 – 3.37 (m, 2H), 2.95 – 2.75 (m, 5H), 2.46 (s, 3H), 2.24 (dd, $J = 9.9, 4.5$ Hz, 2H), 2.07 (d, $J = 8.6$ Hz, 2H), 1.34 – 1.21 (m, 1H), 1.19 – 1.06 (m, 9H), 1.03 (s, 3H).

**EXAMPLE 126**

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (126) Intermediates: **I2**, **P42**, and **S3**. MS (ESI) m/z 1105.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.15 (d, $J = 9.4$ Hz, 1H), 7.70 (dd, $J = 9.4, 2.8$ Hz, 2H), 7.35 (dd, $J = 14.0, 8.3$ Hz, 4H), 7.22 (d, $J = 7.9$ Hz, 2H), 6.86 (d, $J = 8.9$ Hz, 1H), 6.81 – 6.72 (m, 2H), 4.97 (t, $J = 7.6$ Hz, 2H), 4.53 (s, 1H), 4.44 (d, $J = 9.5$ Hz, 1H), 4.34 (t, $J = 12.5$ Hz, 3H), 4.15 (s, 3H), 3.95 (d, $J = 13.2$ Hz, 1H), 3.68 (d, $J = 14.3$ Hz, 10H), 3.39 (d, $J =$

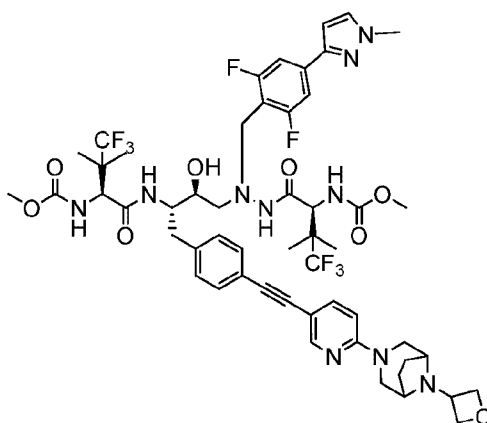
13.9 Hz, 2H), 2.94 – 2.76 (m, 4H), 2.27 – 2.19 (m, 2H), 2.08 (d, $J = 8.5$ Hz, 2H), 1.20 – 1.10 (m, 9H), 1.03 (s, 3H).



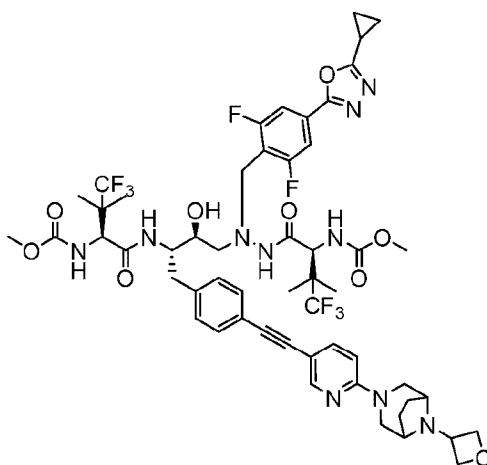
5

EXAMPLE 127

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(4-(oxetan-3-yloxy)pyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (127). Intermediates: **I2**, **P43**, and **S3**. MS (ESI) m/z 1188.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.65 (d, $J = 6.6$ Hz, 1H), 8.32 – 8.26 (m, 1H), 7.70 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.62 – 7.52 (m, 2H), 7.34 (d, $J = 7.9$ Hz, 2H), 7.30 – 7.19 (m, 3H), 6.84 (dd, $J = 21.8, 9.4$ Hz, 1H), 5.76 – 5.64 (m, 1H), 5.11 (t, $J = 6.9$ Hz, 2H), 4.95 (t, $J = 7.6$ Hz, 2H), 4.90 – 4.73 (m, 3H), 4.59 – 4.51 (m, 1H), 4.44 (t, $J = 5.1$ Hz, 1H), 4.32 (td, $J = 14.6, 5.4$ Hz, 3H), 4.25 – 4.12 (m, 4H), 4.05 – 3.95 (m, 1H), 3.68 (d, $J = 17.7$ Hz, 5H), 3.48 – 3.39 (m, 2H), 3.35 (s, 4H), 2.91 (d, $J = 8.2$ Hz, 2H), 2.83 (s, 1H), 2.24 (dd, $J = 9.7, 4.5$ Hz, 2H), 2.07 (d, $J = 8.6$ Hz, 2H), 1.15 (d, $J = 5.7$ Hz, 8H), 1.04 (s, 2H).

**EXAMPLE 128**

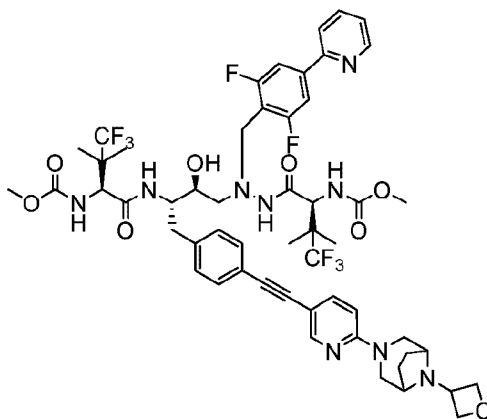
Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(1-methyl-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (128). Intermediates: **12**, **P41**, and **S3**. MS (ESI) m/z 1119.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.29 (d, $J = 2.2$ Hz, 1H), 7.77 – 7.67 (m, 1H), 7.61 (d, $J = 2.3$ Hz, 1H), 7.33 (d, $J = 8.2$ Hz, 4H), 7.22 (d, $J = 8.2$ Hz, 2H), 6.88 (d, $J = 8.9$ Hz, 1H), 6.65 (d, $J = 2.3$ Hz, 1H), 4.95 (t, $J = 7.6$ Hz, 2H), 4.85 (dd, $J = 8.2, 5.1$ Hz, 2H), 4.55 (p, $J = 6.2$ Hz, 1H), 4.45 (d, $J = 8.5$ Hz, 1H), 4.34 (dd, $J = 14.5, 2.5$ Hz, 3H), 4.19 – 4.08 (m, 4H), 3.93 (s, 4H), 3.68 (d, $J = 9.4$ Hz, 6H), 3.48 – 3.39 (m, 2H), 3.35 (s, 1H), 2.99 (s, 1H), 2.94 – 2.73 (m, 5H), 2.27 – 2.19 (m, 2H), 2.08 (t, $J = 6.9$ Hz, 2H), 1.35 – 1.26 (m, 1H), 1.24 – 1.09 (m, 9H), 1.03 (s, 3H).



EXAMPLE 129

Methyl ((5S,8S,9S,14S)-11-(4-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (129).

Intermediates: **I2**, **P40**, and **S3**. MS (ESI) m/z 1147.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.33 – 8.26 (m, 1H), 8.16 (d, J = 9.4 Hz, 1H), 7.70 (dt, J = 9.1, 2.4 Hz, 1H), 7.54 (d, J = 7.3 Hz, 2H), 7.37 – 7.32 (m, 2H), 7.23 (d, J = 8.2 Hz, 2H), 6.91 – 6.77 (m, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.84 (dd, J = 8.2, 5.1 Hz, 2H), 4.59 – 4.52 (m, 1H), 4.52 – 4.40 (m, 1H), 4.39 – 4.24 (m, 3H), 4.22 – 4.13 (m, 4H), 3.96 (d, J = 12.9 Hz, 1H), 3.75 (d, J = 9.0 Hz, 1H), 3.72 – 3.63 (m, 6H), 3.46 – 3.38 (m, 2H), 2.91 (d, J = 8.7 Hz, 2H), 2.88 – 2.74 (m, 2H), 2.36 – 2.20 (m, 3H), 2.08 (d, J = 8.6 Hz, 2H), 1.32 – 1.16 (m, 6H), 1.15 (s, 4H), 1.13 (s, 3H), 1.03 (s, 2H), 0.89 (s, 1H).

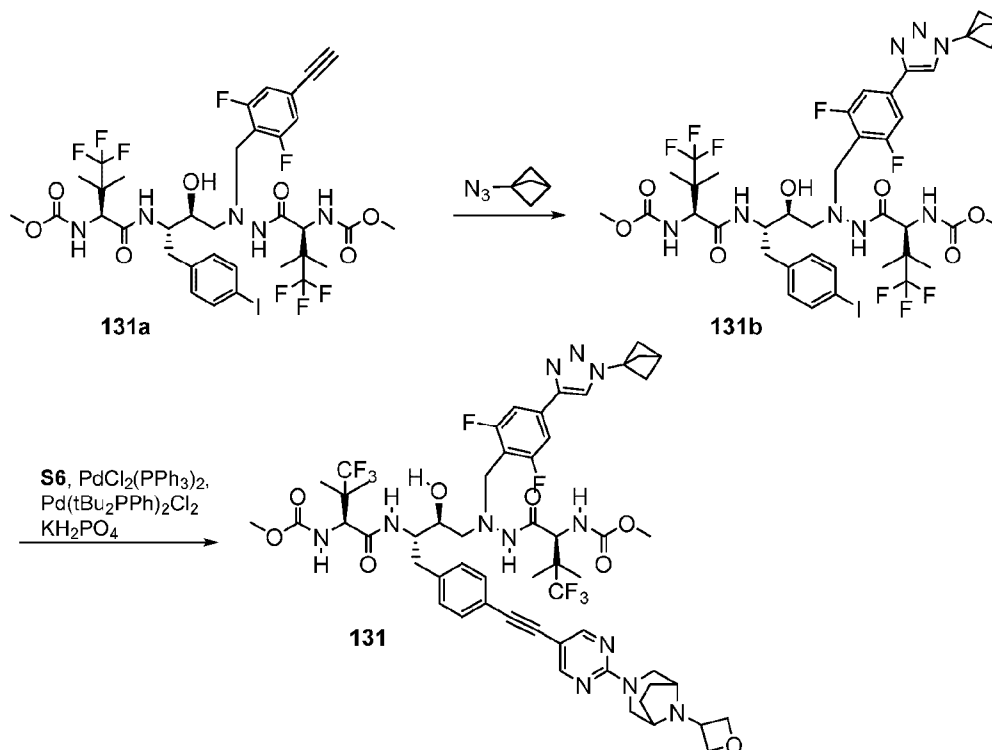
**EXAMPLE 130**

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-

tetraazahexadecan-14-yl)carbamate (130). Intermediates: **I2**, **P28**, and **S3**. MS (ESI) m/z 1116.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.71 (s, 1H), 8.29 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 8.09 (t, J = 7.8 Hz, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.70 (dd, J = 8.8, 2.3 Hz, 1H), 7.64 – 7.52 (m, 3H), 7.34 (d, J = 7.8 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 9.5 Hz, 1H), 6.84 (dd, J = 25.9, 9.4 Hz, 2H), 4.96 (t, J = 7.6 Hz, 2H), 4.83 (dd, J = 8.2, 5.1 Hz, 2H),

4.55 (d, $J = 7.8$ Hz, 1H), 4.48 – 4.41 (m, 1H), 4.35 (dd, $J = 14.5, 2.5$ Hz, 3H), 4.19 – 4.13 (m, 4H), 3.99 (d, $J = 7.6$ Hz, 1H), 3.75 (s, 1H), 3.70 (s, 4H), 3.64 (s, 3H), 3.46 – 3.32 (m, 3H), 2.93 (s, 2H), 2.24 (dd, $J = 9.6, 4.6$ Hz, 2H), 2.07 (d, $J = 8.6$ Hz, 2H), 1.19 – 1.10 (m, 9H), 1.03 (s, 3H).

5

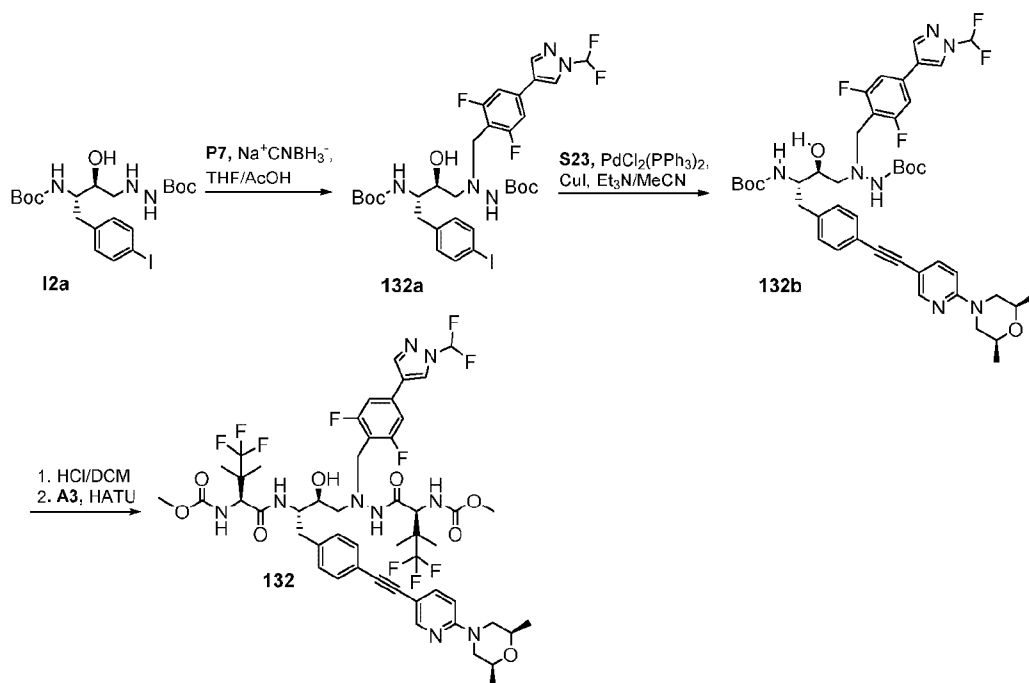
EXAMPLE 131

Methyl ((5S,10S,11S,14S)-8-(4-ethynyl-2,6-difluorobenzyl)-16,16,16-trifluoro-10-hydroxy-11-(4-iodobenzyl)-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,8,12-tetraazahexadecan-14-yl)carbamate (131a). The title compound 131a was prepared according to the method presented for the synthesis of compound 1a but instead utilizing P38. MS (ESI) m/z 924.2 $[M+H]^+$. ¹H NMR (400 MHz, Methanol-d₄) δ 7.52 (d, $J = 8.0$ Hz, 2H), 7.00 (dd, $J = 11.2, 7.8$ Hz, 4H), 4.44 (s, 1H), 4.27 (s, 1H), 4.17 - 4.01 (m, 2H), 3.90 (d, $J = 13.2$ Hz, 1H), 3.71 (t, $J = 5.9$ Hz, 8H), 2.82 (d, $J = 7.8$ Hz, 2H), 2.77 - 2.67 (m, 1H), 1.17 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H).

Methyl ((5S,8S,9S,14S)-11-(4-(1-(bicyclo[1.1.1]pentan-1-yl)-1H-1,2,3-triazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-8-(4-iodobenzyl)-15,15-dimethyl-3,6,13-

trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (131b). To a solution of **131a** (62 mg, 0.07 mmol) in THF (2 mL) was added copper (52 mg, 0.818 mmol), 10% CuSO₄ (100 μ L), and 1-azidobicyclo[1.1.1]pentane in CuSO₄ (0.300 mL, 0.082 mmol). After 2h, added more 1-azidobicyclo[1.1.1]pentane in CuSO₄ (0.300 mL, 0.082 mmol). Stirred for another 2h, added more 1-azidobicyclo[1.1.1]pentane in CuSO₄ (0.300 mL, 0.082 mmol), then stirred for 48h. The reaction was partitioned with EtOAc and brine. The organic extract was washed with NH₄Cl solution and dried over Na₂SO₄ filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (25% - 75% EtOAc/hex to yield **131b**. MS (ESI) m/z 1032.1 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.50 (s, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 6.99 (d, J = 8.1 Hz, 2H), 4.44 (s, 1H), 4.30 (s, 1H), 4.17 - 4.03 (m, 3H), 3.93 (d, J = 13.2 Hz, 1H), 3.71 (s, 4H), 3.66 (s, 3H), 2.86 - 2.67 (m, 5H), 2.45 (s, 7H), 1.16 (s, 4H), 1.14 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H), 0.89 (d, J = 6.7 Hz, 1H).

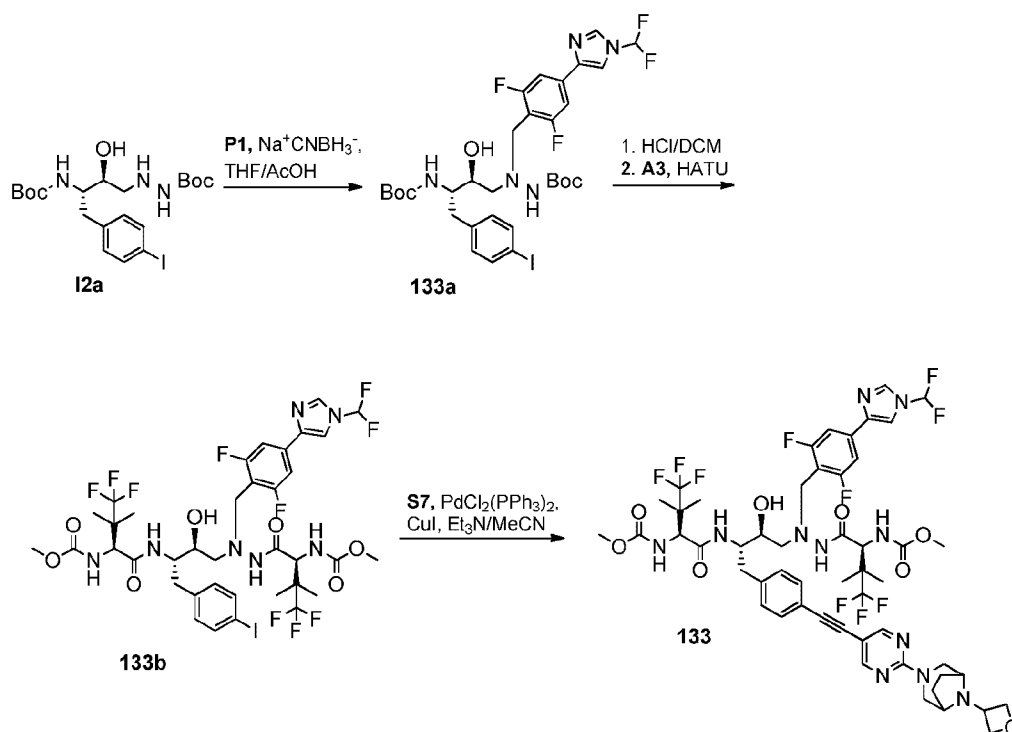
Methyl ((5S,8S,9S,14S)-11-(4-(1-(bicyclo[1.1.1]pentan-1-yl)-1H-1,2,3-triazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (131)
The title compound **131** was prepared according to the method presented for the synthesis of compound **1** but instead utilizing **131b** and **S7**. MS (ESI) m/z 1174.1 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.53 (s, 3H), 8.51 (s, 1H), 8.19 (d, J = 9.4 Hz, 1H), 7.43 (d, J = 8.1 Hz, 3H), 7.34 (d, J = 7.8 Hz, 3H), 7.23 (d, J = 7.8 Hz, 3H), 7.18 (d, J = 9.9 Hz, 1H), 6.83 (d, J = 10.1 Hz, 1H), 4.96 (t, J = 7.6 Hz, 3H), 4.80 (d, J = 7.3 Hz, 6H), 4.44 (d, J = 9.6 Hz, 1H), 4.30 (d, J = 9.9 Hz, 1H), 4.15 (d, J = 6.5 Hz, 5H), 3.94 (d, J = 13.1 Hz, 1H), 3.72 (s, 2H), 3.68 (d, J = 9.6 Hz, 8H), 3.48 (s, 2H), 3.44 (s, 1H), 2.96 - 2.81 (m, 3H), 2.79 (d, J = 10.1 Hz, 1H), 2.74 (s, 1H), 2.45 (s, 8H), 2.21 (d, J = 10.4 Hz, 3H), 1.99 (d, J = 9.2 Hz, 3H), 1.16 (s, 5H), 1.14 (s, 8H), 1.11 (s, 4H), 1.02 (s, 4H).

EXAMPLE 132

- 5 **Synthesis of tert-butyl 2-((2S,3S)-3-((tert-butoxycarbonyl)amino)-2-hydroxy-4-(4-iodophenyl)butyl)-2-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)hydrazine-1-carboxylate (132a).** The title compound **132a** was prepared according to the method presented for the synthesis of compound **1a** but instead utilizing **12a** and **P7**. MS (ESI) m/z 764.0 $[\text{M}+\text{H}]^+$.
- 10 **Synthesis of tert-butyl 2-((2S,3S)-3-((tert-butoxycarbonyl)amino)-4-(4-((6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)ethynyl)phenyl)-2-hydroxybutyl)-2-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)hydrazine-1-carboxylate (132b).** The title compound **132b** was prepared according to the method presented for the synthesis of compound **1** but instead utilizing **132a** and **S23**. MS (ESI) m/z 852.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400
- 15 MHz, Methanol- d_4) δ 8.53 (s, 1H), 8.19 - 8.08 (m, 2H), 7.93 (d, $J = 9.4$ Hz, 1H), 7.50 (t, $J = 59.7$ Hz, 1H), 7.40 (d, $J = 8.2$ Hz, 2H), 7.28 (d, $J = 8.1$ Hz, 5H), 4.07 (d, $J = 12.9$ Hz, 2H), 3.74 (ddd, $J = 10.7, 6.3, 2.5$ Hz, 1H), 3.62 (s, 1H), 2.87 - 2.69 (m, 3H), 1.37 (s, 7H), 1.31 (s, 5H), 1.27 (s, 3H), 1.25 (s, 3H).
- Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-8-(4-((6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)ethynyl)benzyl)-16,16,16-trifluoro-9-**
- 20

hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (132) The title compound **132** was prepared according to the method presented for the synthesis of intermediate **I2** but instead utilizing **132b**. MS (ESI) m/z 1102.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.54 (d, $J = 0.7$ Hz, 1H), 8.25 - 8.10 (m, 3H), 7.83 (d, $J = 9.1$ Hz, 1H), 7.51 (s, 1H), 7.35 (d, $J = 7.3$ Hz, 2H), 7.24 (t, $J = 7.7$ Hz, 4H), 7.15 (dd, $J = 20.4, 9.7$ Hz, 1H), 6.82 (d, $J = 10.0$ Hz, 1H), 4.44 (d, $J = 9.8$ Hz, 1H), 4.31 (d, $J = 9.9$ Hz, 1H), 4.21 - 4.03 (m, 4H), 3.93 (d, $J = 13.2$ Hz, 1H), 3.81 - 3.61 (m, 6H), 2.97 - 2.80 (m, 2H), 2.80 - 2.66 (m, 2H), 2.03 (s, 1H), 1.25 (d, $J = 6.2$ Hz, 6H), 1.17 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H).

10

EXAMPLE 133

Synthesis of tert-butyl 2-((2S,3S)-3-((tert-butoxycarbonyl)amino)-2-hydroxy-4-(4-iodophenyl)butyl)-2-(4-(1-(difluoromethyl)-1H-imidazol-4-yl)-2,6-

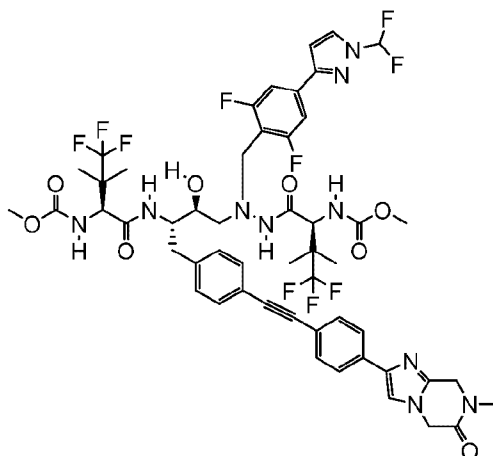
15 difluorobenzyl)hydrazine-1-carboxylate (133a) A mixture of **I2a** (0.28 g, 0.53 mmol) and **P1** (172 mg, 0.67 mmol) were dissolved in a mixture of THF/AcOH (12 mL, 3:1). After stirring at room temperature for 15 min sodium cyanoborohydride (2.49 mmol/gr on resin, 0.44 g, 1.09 mmol) was added. The reaction mixture was stirred overnight, then filtered and the filtered resin was rinsed several times with EtOAc. The combined filtrate was concentrated under reduced

pressure; the residue was recrystallized/precipitated from EtOAc/ hexanes to afford **133a** (351.6 mg, 87.3%). MS (ESI) m/z 764.09 $[M+H]^+$

Synthesis of methyl ((5S,10S,11S,14S)-8-(4-(1-(difluoromethyl)-1H-imidazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-10-hydroxy-11-(4-iodobenzyl)-15,15-dimethyl-3,6,13-

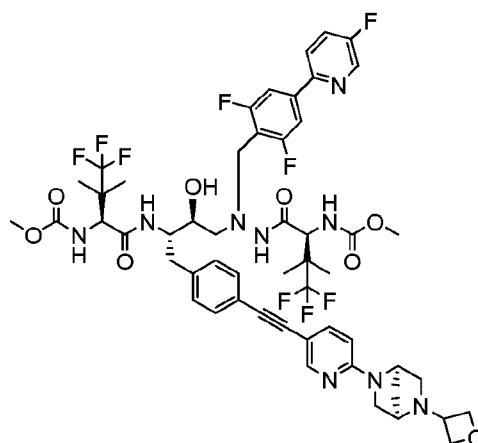
trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,8,12-tetraazahexadecan-14-yl)carbamate (133b). **133a** (75%, 0.3 g, 0.29 mmol) was dissolved in DCM (10 mL) and HCl (4.0M in dioxane, 2.6 mL). The reaction was stirred for 3h then concentrated under reduce pressure the crude material was dissolved in DCM (10 mL) and HATU (0.24 g, 0.64 mmol), N, N-diisopropylethylamine (0.6 mL, 0 mol) was added followed by **A3** (0.21 g, 0.86 mmol). The reaction was stirred at stirred at room temperature overnight. The reaction mixture was diluted with 5 mL of MeOH and concentrated. The crude residue was diluted with EtOAc and washed with 5% LiCl, saturated NaHCO₃, and brine then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (30% to 70%EtOAc/Hex) to afford **133b** (296 mg, 67%). MS (ESI) m/z 1014.6 $[M+H]^+$. ¹H NMR (400 MHz, Methanol-d₄) δ 8.15 (d, J = 1.2 Hz, 1H), 8.01 (d, J = 1.3 Hz, 1H), 7.58 (t, J = 59.9 Hz, 1H), 7.52 (d, J = 7.9 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.2 Hz, 2H), 4.45 (s, 1H), 4.30 (s, 1H), 4.14 (s, 0H), 3.93 (d, J = 13.2 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 2.92 - 2.67 (m, 4H), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H).

Methyl ((5S,10S,11S,14S)-8-(4-(1-(difluoromethyl)-1H-imidazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-10-hydroxy-15,15-dimethyl-11-(4-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,8,12-tetraazahexadecan-14-yl)carbamate (133) In a vial, a solution of **133b** (50 mg, 0.05 mmol), **S7** (17 mg, 0.06 mmol), copper (I) iodide (4.0 mg, 0.02 mmol), trans-Dichlorobis(triphenylphosphine)palladium (II) (99%, 11.1 mg, 0.02 mmol) in a mixture of and MeCN : Et₃N 3:1(1mL) was degassed and then stirred at room temperature overnight. Concentrated under reduced pressure. Purification by HPLC and Lyophilized to give **133**. MS (ESI) m/z 1156.4 $[M+H]^+$. ¹H NMR (400 MHz, Methanol-d₄) δ 8.44 (s, 2H), 8.09 (d, J = 17.5 Hz, 2H), 7.93 (s, 1H), 7.49 (t, J = 60.0 Hz, 1H), 7.27 (dd, J = 18.4, 8.1 Hz, 3H), 7.14 (d, J = 8.0 Hz, 2H), 6.73 (d, J = 9.9 Hz, 1H), 4.86 (d, J = 7.6 Hz, 2H), 4.72 (dd, J = 8.2, 5.0 Hz, 2H), 4.35 (d, J = 8.7 Hz, 1H), 4.22 (d, J = 9.8 Hz, 1H), 4.03 (d, J = 12.8 Hz, 4H), 3.84 (d, J = 13.2 Hz, 1H), 3.58 (d, J = 8.6 Hz, 5H), 3.37 (d, J = 14.4 Hz, 2H), 2.90 - 2.62 (m, 4H), 2.56 (s, 1H), 2.12 (d, J = 11.1 Hz, 2H), 1.90 (d, J = 9.0 Hz, 2H), 1.07 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H).

**EXAMPLE 134**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-

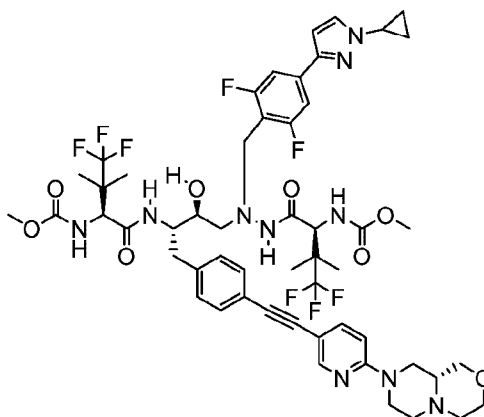
- 16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((4-(7-methyl-6-oxo-5,6,7,8-**
tetrahydroimidazo[1,2-a]pyrazin-2-yl)phenyl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-
trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate
 Intermediates: **P4**, **A3**, and **S5**. MS (ESI) m/z 1137.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol-
 d4) δ 8.11 (d, $J = 9.4$ Hz, 1H), 8.01 (d, $J = 2.7$ Hz, 1H), 7.75 - 7.50 (m, 6H), 7.46 (d, $J = 16.5$ Hz,
 2H), 7.36 (d, $J = 8.2$ Hz, 2H), 7.28 (d, $J = 9.5$ Hz, 3H), 7.15 (d, $J = 8.0$ Hz, 3H), 6.85 (d, $J = 2.7$
 Hz, 1H), 6.73 (d, $J = 10.0$ Hz, 1H), 4.79 - 4.71 (m, 5H), 4.35 (d, $J = 9.9$ Hz, 1H), 4.22 (d, $J =$
 10.0 Hz, 1H), 4.06 (d, $J = 13.5$ Hz, 3H), 3.85 (d, $J = 13.0$ Hz, 1H), 3.65 (s, 2H), 3.61 (s, 3H),
 3.57 (s, 3H), 3.08 (s, 4H), 2.83 (d, $J = 8.0$ Hz, 2H), 2.73 - 2.62 (m, 1H), 1.07 (s, 4H), 1.05 (s,
 3H), 1.02 (s, 4H), 0.94 (s, 3H).



EXAMPLE 135

Methyl ((5S,10S,11S,14S)-8-(2,6-difluoro-4-(5-fluoropyridin-2-yl)benzyl)-16,16,16-trifluoro-10-hydroxy-15,15-dimethyl-11-(4-(((6-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,8,12-tetraazahexadecan-14-yl)carbamate(135).

Intermediates: **P14**, **A3**, and **S6**. MS (ESI) m/z 1120.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.46 (d, $J = 2.9$ Hz, 1H), 8.16 (d, $J = 2.1$ Hz, 1H), 8.11 (d, $J = 9.2$ Hz, 1H), 7.87 (dd, $J = 8.8, 4.3$ Hz, 1H), 7.65 - 7.55 (m, 2H), 7.51 (d, $J = 8.7$ Hz, 2H), 7.23 (d, $J = 7.9$ Hz, 2H), 7.13 (d, $J = 8.1$ Hz, 3H), 6.74 (d, $J = 10.0$ Hz, 1H), 6.57 (d, $J = 8.8$ Hz, 1H), 4.95 (s, 1H), 4.86 (dd, $J = 8.4, 6.3$ Hz, 1H), 4.61 (s, 1H), 4.49 (dq, $J = 11.2, 6.0, 5.5$ Hz, 2H), 4.41 (s, 1H), 4.35 (d, $J = 9.7$ Hz, 1H), 4.21 (d, $J = 10.0$ Hz, 1H), 4.07 (d, $J = 13.3$ Hz, 2H), 3.87 (d, $J = 13.1$ Hz, 1H), 3.74 - 3.62 (m, 2H), 3.60 (s, 3H), 3.55 (s, 3H), 2.87 - 2.73 (m, 3H), 2.73 - 2.65 (m, 1H), 2.23 (s, 2H), 1.06 (d, $J = 5.4$ Hz, 6H), 1.02 (s, 3H), 0.93 (s, 3H).

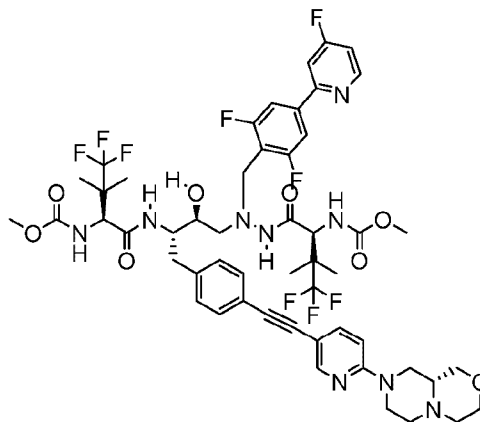
**EXAMPLE 136**

methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-8-(4-(((6-((R)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)pyridin-3-yl)ethynyl)benzyl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (136).

Intermediates: **P13**, **A3**, and **S8**. MS (ESI) m/z 1118.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.22 (d, $J = 2.3$ Hz, 1H), 8.10 (d, $J = 9.4$ Hz, 1H), 7.61 (dt, $J = 5.4, 2.6$ Hz, 2H), 7.59 - 7.50 (m, 1H), 7.47 (dt, $J = 7.7, 4.1$ Hz, 1H), 7.30 - 7.19 (m, 4H), 7.13 (d, $J = 8.1$ Hz, 2H), 7.06 (s, 0H), 6.86 (d, $J = 8.9$ Hz, 1H), 6.72 (d, $J = 9.9$ Hz, 1H), 6.55 (d, $J = 2.5$ Hz, 1H), 4.53 (dd, $J =$

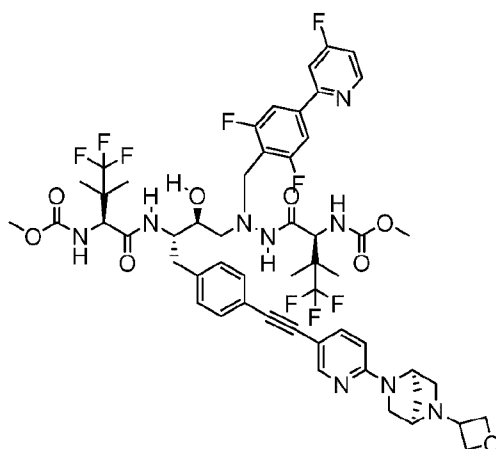
22.7, 13.2 Hz, 2H), 4.42 - 4.30 (m, 1H), 4.26 - 4.18 (m, 1H), 4.03 (d, J = 13.2 Hz, 4H), 3.84 (d, J = 13.1 Hz, 1H), 3.76 (t, J = 12.7 Hz, 1H), 3.59 (d, J = 9.3 Hz, 6H), 3.49 (d, J = 11.0 Hz, 1H), 3.44 - 3.35 (m, 0H), 2.81 (d, J = 7.3 Hz, 3H), 2.72 - 2.63 (m, 1H), 1.08 (s, 3H), 1.05 (s, 4H), 1.04 (d, J = 2.8 Hz, 0H), 1.02 (s, 2H), 1.00 - 0.95 (m, 1H), 0.94 (s, 3H).

5



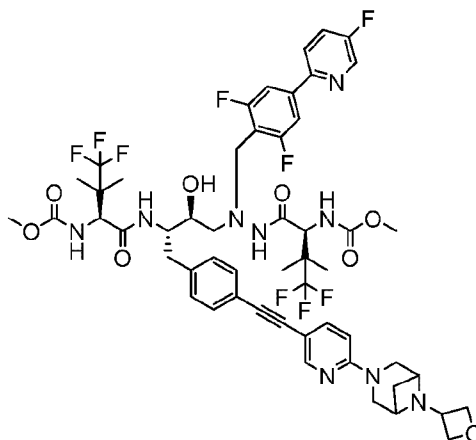
EXAMPLE 137

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(4-fluoropyridin-2-yl)benzyl)-16,16,16-trifluoro-8-(4-((6-((R)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)pyridin-3-yl)ethynyl)benzyl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (137). Intermediates: **P15**, **A3**, and **S8**. MS (ESI) m/z 1118.6 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.56 (dd, J = 8.6, 5.6 Hz, 1H), 8.21 (d, J = 2.2 Hz, 1H), 8.11 (d, J = 9.3 Hz, 1H), 7.67 (dd, J = 10.3, 2.4 Hz, 1H), 7.61 (dd, J = 8.9, 2.2 Hz, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 7.16 - 7.08 (m, 3H), 6.86 (d, J = 8.9 Hz, 1H), 6.74 (d, J = 10.0 Hz, 1H), 4.52 (dd, J = 23.4, 12.6 Hz, 2H), 4.35 (d, J = 10.0 Hz, 1H), 4.21 (d, J = 9.9 Hz, 1H), 4.07 (t, J = 10.4 Hz, 4H), 3.87 (d, J = 13.2 Hz, 1H), 3.75 (t, J = 12.6 Hz, 1H), 3.64 (s, 1H), 3.60 (s, 3H), 3.55 (s, 2H), 3.48 (d, J = 10.7 Hz, 1H), 3.39 (t, J = 10.4 Hz, 1H), 2.88 - 2.73 (m, 4H), 2.73 - 2.64 (m, 1H), 1.06 (d, J = 5.6 Hz, 6H), 1.02 (s, 3H), 0.93 (s, 3H).

**EXAMPLE 138**

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(4-fluoropyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (138). Intermediates: **P15**, **A3**, and **S6**. MS (ESI) m/z 1120.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.56 (dd, J = 8.6, 5.6 Hz, 1H), 8.16 (s, 1H), 8.11 (d, J = 9.5 Hz, 1H), 7.68 (d, J = 9.4 Hz, 1H), 7.58 (dd, J = 14.3, 8.7 Hz, 3H), 7.23 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 8.0 Hz, 4H), 6.74 (d, J = 10.2 Hz, 1H), 6.57 (d, J = 8.8 Hz, 1H), 4.95 (s, 1H), 4.61 (s, 1H), 4.49 (dd, J = 11.6, 6.4 Hz, 1H), 4.41 (s, 1H), 4.35 (d, J = 10.0 Hz, 1H), 4.21 (d, J = 9.9 Hz, 1H), 4.08 (d, J = 12.8 Hz, 2H), 3.87 (d, J = 13.0 Hz, 1H), 3.66 (d, J = 16.3 Hz, 2H), 3.60 (d, J = 1.1 Hz, 3H), 3.55 (s, 3H), 2.81 (d, J = 7.8 Hz, 2H), 2.71 (d, J = 9.5 Hz, 1H), 2.23 (s, 2H), 1.06 (d, J = 4.6 Hz, 6H), 1.02 (s, 3H), 0.93 (s, 3H).

15

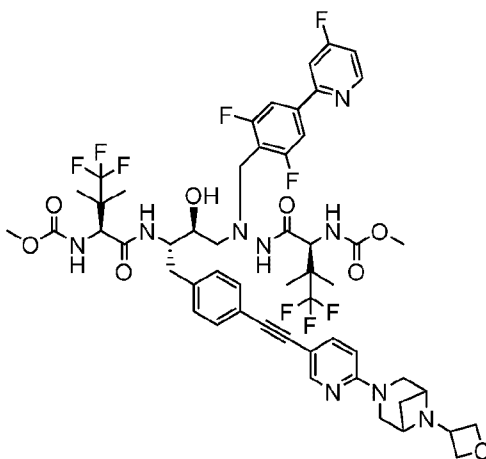


EXAMPLE 139

Methyl ((5S,10S,11S,14S)-8-(2,6-difluoro-4-(5-fluoropyridin-2-yl)benzyl)-16,16,16-trifluoro-10-hydroxy-15,15-dimethyl-11-(4-((6-(6-(oxetan-3-yl)-3,6-

5 diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,8,12-tetraazahexadecan-14-yl)carbamate (139).

Intermediates: **P14**, **A3**, and **S4**. MS (ESI) m/z 1120.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.46 (d, $J = 2.9$ Hz, 1H), 8.24 (d, $J = 2.3$ Hz, 1H), 8.10 (d, $J = 9.3$ Hz, 1H), 7.96 - 7.86 (m, 1H), 7.65 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.59 (td, $J = 8.5, 3.0$ Hz, 1H), 7.51 (d, $J = 8.6$ Hz, 2H), 7.24 (d, $J = 7.9$ Hz, 2H), 7.13 (d, $J = 8.0$ Hz, 2H), 7.08 (d, $J = 9.9$ Hz, 1H), 6.73 (d, $J = 10.6$ Hz, 1H), 6.69 (d, $J = 8.9$ Hz, 1H), 4.96 - 4.83 (m, 4H), 4.59 - 4.47 (m, 2H), 4.42 - 4.31 (m, 1H), 4.31 - 4.19 (m, 1H), 4.07 (d, $J = 13.4$ Hz, 4H), 3.87 (d, $J = 13.2$ Hz, 1H), 3.64 (s, 2H), 3.60 (s, 3H), 3.56 (s, 3H), 2.82 (d, $J = 8.4$ Hz, 2H), 2.74 - 2.65 (m, 1H), 2.02 (d, $J = 11.0$ Hz, 1H), 1.07 (s, 4H), 1.06 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H).



15

EXAMPLE 140

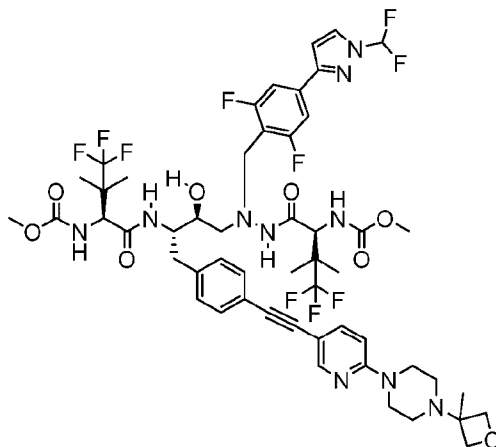
Methyl ((5S,10S,11S,14S)-8-(2,6-difluoro-4-(4-fluoropyridin-2-yl)benzyl)-16,16,16-trifluoro-10-hydroxy-15,15-dimethyl-11-(4-((6-(6-(oxetan-3-yl)-3,6-

20 diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,8,12-tetraazahexadecan-14-yl)carbamate (140).

Intermediates: **P15**, **A3**, and **S4**. MS (ESI) m/z 1120.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.66 (dd, $J = 8.6, 5.6$ Hz, 1H), 8.33 (s, 1H), 8.21 (d, $J = 9.3$ Hz, 1H), 7.76 (t, $J = 9.9$ Hz, 2H), 7.66 (d, $J = 8.5$ Hz, 2H), 7.34 (d, $J = 7.8$ Hz, 2H), 7.23 (d, $J = 7.7$ Hz, 3H), 6.84 (d, $J = 10.1$

Hz, 0H), 6.78 (d, J = 8.9 Hz, 1H), 4.61 (dd, J = 8.2, 4.0 Hz, 2H), 4.45 (d, J = 10.0 Hz, 1H), 4.31 (d, J = 10.0 Hz, 1H), 4.18 (d, J = 12.4 Hz, 2H), 3.99 (s, 0H), 3.74 (s, 2H), 3.70 (s, 3H), 3.65 (s, 2H), 2.91 (d, J = 8.1 Hz, 2H), 2.80 (d, J = 9.8 Hz, 1H), 2.11 (d, J = 10.9 Hz, 1H), 1.33 - 1.23 (m, 1H), 1.16 (s, 4H), 1.15 (s, 3H), 1.12 (s, 2H), 1.03 (s, 3H).

5

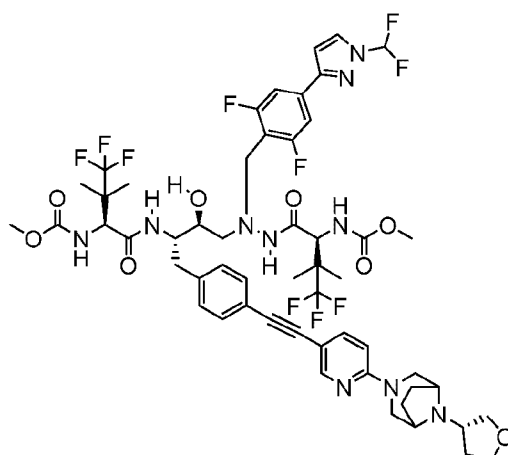


EXAMPLE 141

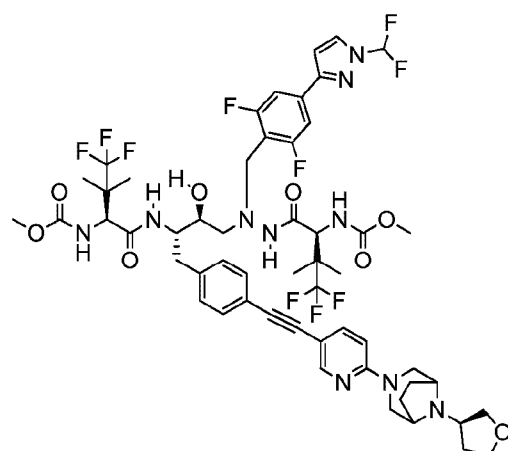
methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-

16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(4-(3-methyloxetan-3-yl)piperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (141). Intermediates: **P4**, **A3**, and **S10**. MS (ESI) m/z 1143 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.12 (d, J = 2.3 Hz, 1H), 8.08 (d, J = 9.4 Hz, 1H), 8.01 (d, J = 2.7 Hz, 1H), 7.62 - 7.42 (m, 3H), 7.36 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 9.9 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.72 (dd, J = 9.5, 5.4 Hz, 2H), 4.56 (d, J = 5.9 Hz, 2H), 4.34 (d, J = 9.9 Hz, 1H), 4.27 - 4.15 (m, 3H), 4.05 (d, J = 12.1 Hz, 2H), 3.85 (d, J = 13.1 Hz, 1H), 3.64 (s, 2H), 3.60 (s, 3H), 3.56 (d, J = 8.7 Hz, 7H), 2.75 (dd, J = 44.1, 8.8 Hz, 4H), 2.46 (t, J = 5.0 Hz, 4H), 1.32 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H).

20

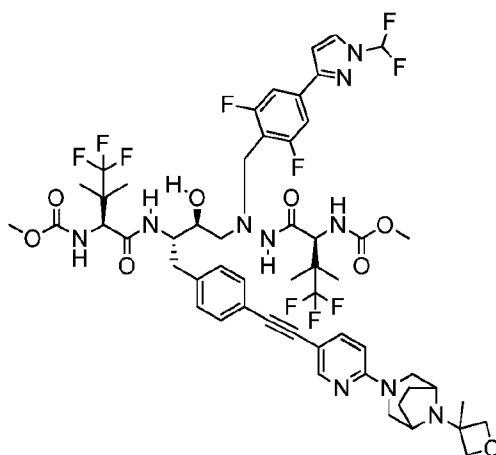
**EXAMPLE 142**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-(4-((6-(8-((S)-tetrahydrofuran-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (142). Intermediates: **P4**, **A3**, and **S11**. MS (ESI) m/z 1170.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.29 (d, $J = 2.3$ Hz, 1H), 8.17 (d, $J = 9.4$ Hz, 1H), 8.10 (d, $J = 2.7$ Hz, 1H), 7.76 - 7.60 (m, 2H), 7.60 - 7.52 (m, 1H), 7.45 (d, $J = 8.2$ Hz, 2H), 7.33 (d, $J = 7.8$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 9.8$ Hz, 1H), 6.94 (d, $J = 2.7$ Hz, 1H), 6.84 (d, $J = 8.9$ Hz, 1H), 6.79 (d, $J = 10.0$ Hz, 1H), 4.45 (s, 0H), 4.42 - 4.27 (m, 2H), 4.23 (s, 1H), 4.20 - 4.05 (m, 2H), 4.05 - 3.89 (m, 3H), 3.88 - 3.56 (m, 8H), 3.06 - 2.85 (m, 3H), 2.85 - 2.69 (m, 1H), 2.50 (d, $J = 12.5$ Hz, 1H), 2.32 (s, 2H), 2.22 - 2.00 (m, 3H), 1.16 (s, 4H), 1.14 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H).



EXAMPLE 143

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-((6-(8-((R)-tetrahydrofuran-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (143). Intermediates: **P4**, **A3**, and **S12**. MS (ESI) m/z 1170.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.29 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 9.3 Hz, 1H), 8.10 (d, J = 2.7 Hz, 1H), 7.74 - 7.60 (m, 2H), 7.59 - 7.50 (m, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 9.7 Hz, 1H), 6.94 (d, J = 2.7 Hz, 1H), 6.84 (d, J = 8.9 Hz, 1H), 6.79 (d, J = 9.9 Hz, 1H), 4.44 (d, J = 10.1 Hz, 1H), 4.30 (d, J = 9.9 Hz, 1H), 4.23 (s, 1H), 4.14 (d, J = 12.3 Hz, 2H), 3.97 (t, J = 14.4 Hz, 1H), 3.86 - 3.57 (m, 8H), 2.97 - 2.84 (m, 3H), 2.84 - 2.68 (m, 1H), 2.49 (s, 1H), 2.32 (s, 2H), 2.22 - 2.04 (m, 3H), 1.16 (s, 4H), 1.14 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H).

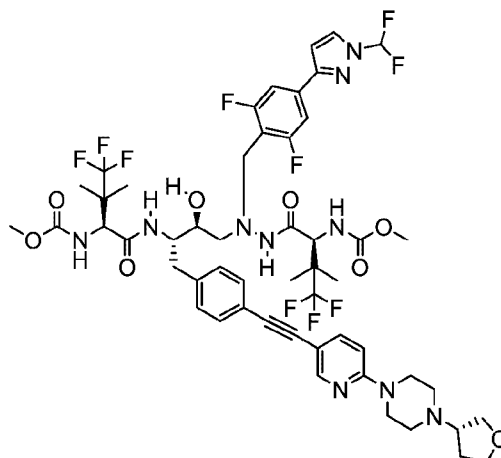


15

EXAMPLE 144

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(3-methyloxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (144). Intermediates: **P4**, **A3**, and **S13**. MS (ESI) m/z 1170.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.23 - 8.13 (m, 1H), 8.10 (d, J = 2.8 Hz, 1H), 7.57 (dd, J = 8.9, 2.4 Hz, 1H), 7.53 (t, J = 59.8 Hz, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 6.94

(d, J = 2.7 Hz, 1H), 6.69 (d, J = 9.0 Hz, 1H), 4.43 (s, 1H), 4.30 (s, 1H), 4.14 (d, J = 12.1 Hz, 2H), 3.95 (d, J = 13.2 Hz, 1H), 3.84 (dt, J = 8.2, 4.5 Hz, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 3.49 (d, J = 7.1 Hz, 1H), 3.39 (s, 1H), 3.11 (dt, J = 11.9, 2.1 Hz, 2H), 2.90 (d, J = 8.0 Hz, 2H), 2.83 - 2.76 (m, 1H), 2.73 (d, J = 5.0 Hz, 1H), 2.69 (s, 0H), 2.62 (d, J = 4.9 Hz, 1H), 2.46 (d, J = 13.4 Hz, 1H), 1.97 (s, 2H), 1.67 (d, J = 9.0 Hz, 2H), 1.43 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H).

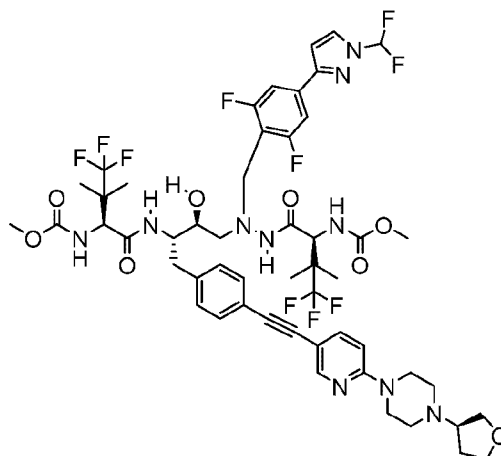


10

EXAMPLE 145

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-(4-((6-(4-((S)-tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (145).

15 Intermediates: **P4**, **A3**, and **S15**. MS (ESI) m/z 1143.5 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.36 - 8.26 (m, 1H), 8.19 (d, J = 9.2 Hz, 1H), 8.11 (d, J = 2.7 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.69 (d, J = 2.1 Hz, 1H), 7.67 - 7.61 (m, 0H), 7.57 (dd, J = 7.3, 3.3 Hz, 1H), 7.54 (s, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.15 (s, 1H), 6.99 - 6.86 (m, 2H), 6.81 (d, J = 10.1 Hz, 1H), 4.45 (s, 0H), 4.31 (d, J = 10.0 Hz, 1H), 4.26 - 4.02 (m, 5H), 4.00 - 3.82 (m, 3H), 3.75 (d, J = 8.4 Hz, 1H), 3.68 (d, J = 10.9 Hz, 6H), 2.97 - 2.85 (m, 3H), 2.55 - 2.35 (m, 1H), 2.28 - 2.16 (m, 1H), 1.16 (s, 4H), 1.15 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H).

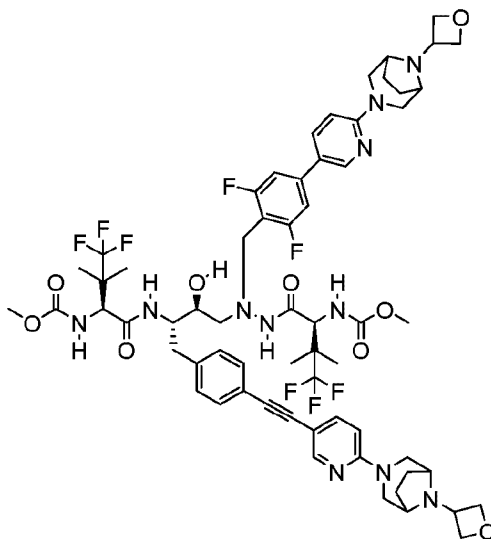


EXAMPLE 146

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-

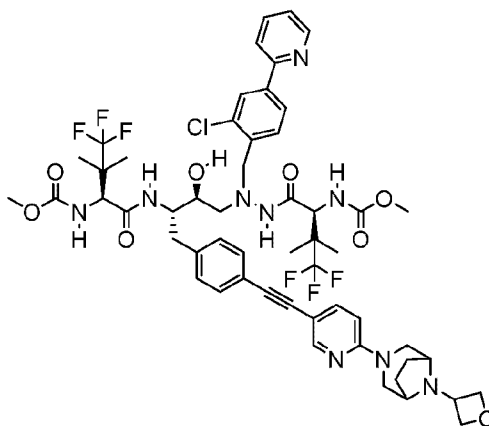
5 16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-(4-((6-(4-((R)-tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (146).

Intermediates: **P4**, **A3**, and **S14**. MS (ESI) m/z 1143.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol-
 10 d_4) δ 8.30 (d, $J = 2.3$ Hz, 1H), 8.19 (d, $J = 9.1$ Hz, 1H), 8.11 (d, $J = 2.8$ Hz, 1H), 7.71 (d, $J = 2.4$
 Hz, 0H), 7.69 (s, 1H), 7.68 - 7.61 (m, 1H), 7.60 - 7.55 (m, 1H), 7.54 (s, 1H), 7.45 (d, $J = 8.2$ Hz,
 2H), 7.33 (d, $J = 7.8$ Hz, 2H), 7.23 (d, $J = 8.1$ Hz, 3H), 6.96 - 6.85 (m, 2H), 6.81 (d, $J = 9.9$ Hz,
 1H), 4.44 (d, $J = 9.8$ Hz, 1H), 4.31 (d, $J = 10.0$ Hz, 1H), 4.23 - 4.07 (m, 4H), 3.95 (d, $J = 13.3$
 Hz, 1H), 3.92 - 3.86 (m, 1H), 3.75 (d, $J = 8.2$ Hz, 2H), 3.69 (s, 4H), 3.66 (s, 3H), 3.00 - 2.82 (m,
 3H), 2.79 (d, $J = 10.0$ Hz, 1H), 2.42 (s, 0H), 2.21 (d, $J = 8.5$ Hz, 0H), 1.16 (s, 5H), 1.15 (s, 3H),
 15 1.12 (s, 3H), 1.03 (s, 3H).

**EXAMPLE 147**

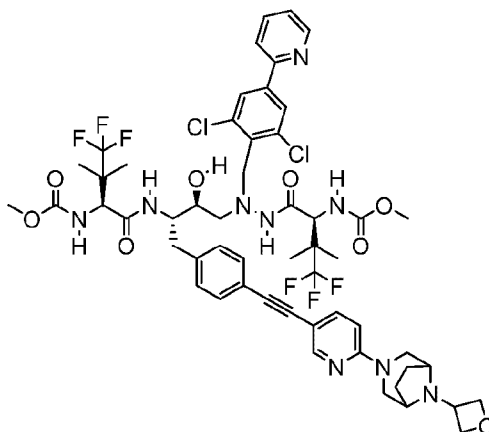
Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (147).

Intermediates: **P22**, **A3**, and **S3**. MS (ESI) m/z 1282.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.43 - 8.31 (m, 1H), 8.20 (d, J = 2.3 Hz, 1H), 7.84 (d, J = 9.0 Hz, 1H), 7.60 (dd, J = 8.8, 2.3 Hz, 1H), 7.24 (d, J = 7.9 Hz, 2H), 7.17 - 7.04 (m, 4H), 6.86 (d, J = 9.0 Hz, 1H), 6.77 (d, J = 8.9 Hz, 1H), 6.71 (d, J = 10.0 Hz, 1H), 4.87 (t, J = 7.7 Hz, 4H), 4.74 - 4.68 (m, 4H), 4.37 - 4.17 (m, 6H), 4.10 - 3.99 (m, 6H), 3.86 (d, J = 13.1 Hz, 1H), 3.67 - 3.62 (m, 1H), 3.60 (s, 3H), 3.56 (s, 3H), 3.34 - 3.25 (m, 5H), 2.81 (d, J = 7.7 Hz, 2H), 2.74 - 2.65 (m, 1H), 2.19 - 2.10 (m, 4H), 2.03 - 1.93 (m, 4H), 1.07 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H).

**EXAMPLE 148**

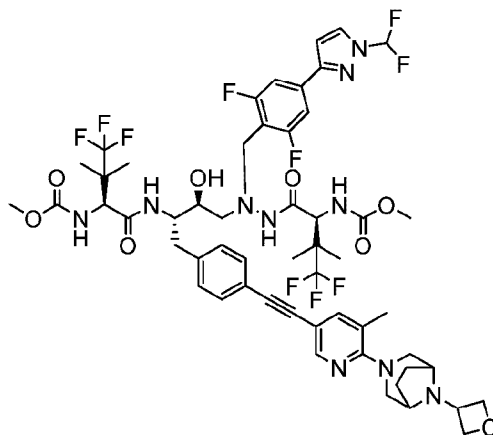
Methyl ((5S,8S,9S,14S)-11-(2-chloro-4-(pyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (148). Intermediates: **P25**, **A3**, and **S3**. MS (ESI) m/z 1114.7 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.55 (d, $J = 5.0$ Hz, 1H), 8.20 (d, $J = 2.1$ Hz, 1H), 8.04 (d, $J = 9.5$ Hz, 1H), 7.94 - 7.85 (m, 1H), 7.82 (d, $J = 8.1$ Hz, 1H), 7.77 - 7.70 (m, 1H), 7.65 (d, $J = 8.1$ Hz, 1H), 7.60 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.42 - 7.32 (m, 1H), 7.24 (d, $J = 7.9$ Hz, 2H), 7.13 (d, $J = 8.0$ Hz, 2H), 6.77 (d, $J = 8.8$ Hz, 1H), 6.71 (d, $J = 10.3$ Hz, 1H), 4.87 (t, $J = 7.6$ Hz, 2H), 4.73 - 4.66 (m, 2H), 4.31 (d, $J = 10.0$ Hz, 1H), 4.18 (d, $J = 9.7$ Hz, 1H), 4.14 - 4.03 (m, 3H), 3.99 (d, $J = 14.2$ Hz, 1H), 3.74 - 3.66 (m, 1H), 3.58 (s, 3H), 3.48 (s, 3H), 3.29 (s, 1H), 2.87 - 2.68 (m, 2H), 2.21 - 2.07 (m, 1H), 2.03 - 1.93 (m, 2H), 1.05 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H), 0.84 (s, 3H).

15



EXAMPLE 149

Methyl ((5S,8S,9S,14S)-11-(2,6-dichloro-4-(pyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (149). Intermediates: **P24**, **A3**, and **S3**. MS (ESI) m/z 1148.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.56 (d, $J = 5.0$ Hz, 1H), 8.20 (d, $J = 2.2$ Hz, 1H), 8.04 (d, $J = 9.4$ Hz, 1H), 7.88 (s, 2H), 7.83 (d, $J = 7.8$ Hz, 2H), 7.64 - 7.54 (m, 1H), 7.33 (t, $J = 5.7$ Hz, 1H), 7.23 (d, $J = 7.7$ Hz, 2H), 7.12 (d, $J = 8.0$ Hz, 2H), 6.77 (d, $J = 8.9$ Hz, 1H), 6.71 (d, $J = 10.1$ Hz, 1H), 4.87 (t, $J = 7.5$ Hz, 2H), 4.71 (dd, $J = 8.2, 4.9$ Hz, 2H), 4.36 - 4.23 (m, 2H), 4.20 (d, $J = 9.9$ Hz, 1H), 4.12 - 3.98 (m, 4H), 3.69 - 3.62 (m, 1H), 3.59 (s, 3H), 3.54 (s, 3H), 3.29 (s, 1H), 2.83 - 2.75 (m, 2H), 2.72 - 2.62 (m, 1H), 2.17 - 2.08 (m, 1H), 2.03 - 1.93 (m, 2H), 1.05 (s, 6H), 0.99 (s, 3H), 0.89 (s, 3H).



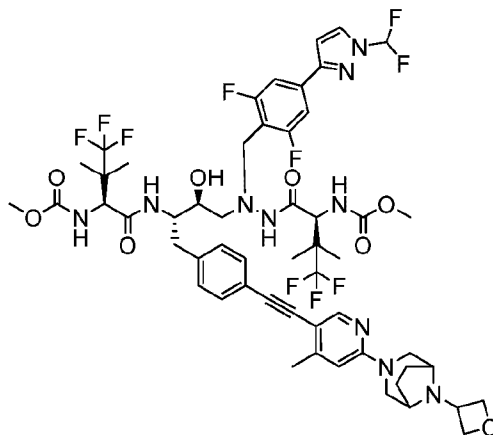
15

EXAMPLE 150

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((5-methyl-6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (150). Intermediates: **P4**, **A3**, and **S44**. MS (ESI) m/z 1171.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.17 (d, $J = 2.2$ Hz, 1H), 8.07 (d, $J = 9.4$ Hz, 1H), 8.01 (d, $J = 2.7$ Hz, 1H), 7.61 - 7.55 (m, 3H), 7.44 (s, 1H), 7.35 (d, $J = 8.3$ Hz, 2H), 7.30 - 7.22 (m, 2H), 7.14 (d, $J = 8.0$ Hz, 2H), 7.02 (d, $J = 9.9$ Hz, 1H), 6.84 (d, $J = 2.8$ Hz, 1H), 6.69 (d, $J = 9.9$ Hz, 1H), 4.88 - 4.80 (m, 2H), 4.73 - 4.68 (m, 2H), 4.41 (s, 1H), 4.34 (d, $J = 9.9$ Hz, 1H), 4.21 (d, $J = 10.0$ Hz, 1H), 4.10 - 3.98 (m,

4H), 3.85 (d, J = 13.2 Hz, 1H), 3.64 (s, 1H), 3.59 (s, 3H), 3.57 (s, 3H), 3.48 (d, J = 13.5 Hz, 2H), 3.38 (d, J = 1.7 Hz, 1H), 3.35 (s, 1H), 3.25 (s, 1H), 2.85 - 2.74 (m, 3H), 2.72 - 2.65 (m, 1H), 2.27 (s, 5H), 2.17 - 2.11 (m, 2H), 1.06 (d, J = 6.7 Hz, 6H), 1.02 (s, 3H), 0.93 (s, 3H). ¹⁹F NMR (377 MHz, Methanol-d₄) δ -77.38, -77.71, -77.88, -96.97 (dd, J = 59.8, 18.8 Hz), -114.92.

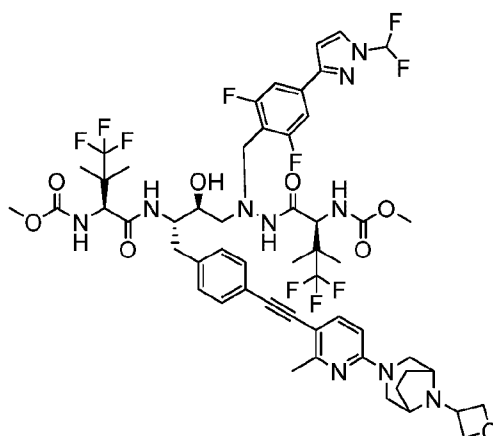
5



EXAMPLE 151

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((4-methyl-6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (151).

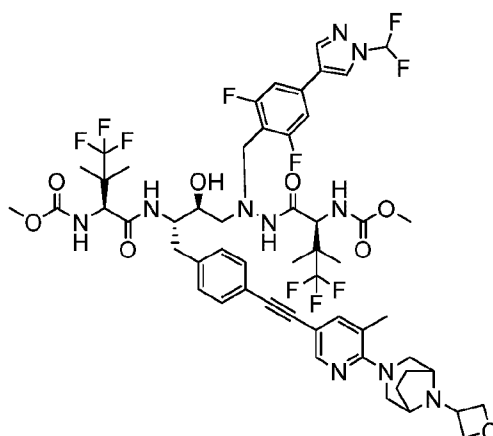
Intermediates: **P4**, **A3**, and **S46**. MS (ESI) m/z 1171.3 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.20 (s, 1H), 8.17 (d, J = 9.3 Hz, 1H), 8.10 (d, J = 2.7 Hz, 1H), 7.68 (s, 0H), 7.53 (s, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.38 (s, 0H), 7.34 (d, J = 7.8 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 9.8 Hz, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.82 (s, 0H), 6.79 (s, 1H), 4.99 - 4.89 (m, 2H), 4.83 - 4.77 (m, 2H), 4.51 (s, 1H), 4.47 - 4.42 (m, 1H), 4.35 (s, 1H), 4.31 (s, 1H), 4.29 (s, 0H), 4.16 (s, 1H), 4.13 (s, 3H), 3.95 (d, J = 13.2 Hz, 1H), 3.74 (s, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.38 (s, 1H), 3.34 (s, 3H), 2.94 - 2.84 (m, 3H), 2.78 (dd, J = 12.5, 9.0 Hz, 1H), 2.44 (s, 3H), 2.25 - 2.18 (m, 2H), 2.10 - 2.04 (m, 2H), 1.16 (s, 4H), 1.13 (d, J = 12.7 Hz, 7H), 1.02 (s, 3H). ¹⁹F NMR (377 MHz, Methanol-d₄) δ -77.38, -77.71, -77.82, -96.97 (dd, J = 59.8, 18.6 Hz), -114.92

**EXAMPLE 152**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-

5 **16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-methyl-6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (152).**

Intermediates: **P4**, **A3**, and **S45**. MS (ESI) m/z 1170.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol-
 10 d_4) δ 8.17 (d, $J = 9.3$ Hz, 1H), 8.10 (d, $J = 2.7$ Hz, 1H), 7.68 (s, 0H), 7.62 (d, $J = 8.7$ Hz, 1H),
 7.53 (s, 1H), 7.45 (d, $J = 8.2$ Hz, 2H), 7.38 (s, 0H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.22 (d, $J = 8.1$ Hz,
 2H), 7.11 (d, $J = 9.9$ Hz, 1H), 6.93 (d, $J = 2.8$ Hz, 1H), 6.80 (d, $J = 9.8$ Hz, 1H), 6.67 (d, $J = 8.8$
 Hz, 1H), 4.96 (dd, $J = 8.2, 7.0$ Hz, 2H), 4.81 (dd, $J = 8.2, 5.1$ Hz, 2H), 4.51 (s, 1H), 4.47 - 4.43
 (m, 1H), 4.38 (d, $J = 13.8$ Hz, 2H), 4.32 - 4.27 (m, 1H), 4.15 (d, $J = 12.2$ Hz, 4H), 3.95 (d, $J =$
 13.1 Hz, 1H), 3.73 (s, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.38 - 3.35 (m, 1H), 3.34 - 3.32 (m, 1H),
 15 2.88 (dd, $J = 18.8, 5.2$ Hz, 3H), 2.78 (dd, $J = 12.5, 9.0$ Hz, 1H), 2.56 (s, 3H), 2.25 - 2.18 (m, 2H),
 2.08 (t, $J = 6.8$ Hz, 2H), 1.16 (s, 5H), 1.13 (d, $J = 13.1$ Hz, 7H), 1.02 (s, 3H). ^{19}F NMR (377
 MHz, Methanol- d_4) δ -77.39, -77.71, -77.86, -96.97 (dd, $J = 59.9, 18.5$ Hz), -114.92

**EXAMPLE 153**

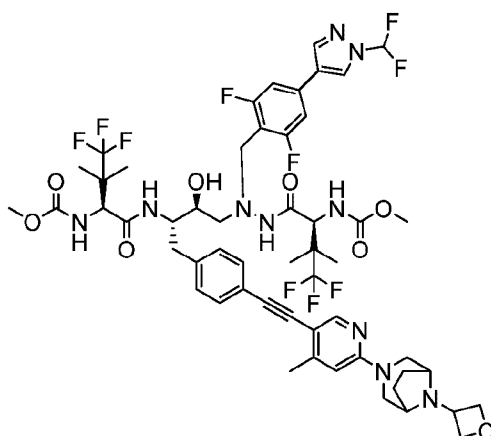
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-

16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((5-methyl-6-(8-(oxetan-3-yl)-3,8-

5 diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-
2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (153).

Intermediates: **P7**, **A3**, and **S44**. MS (ESI) m/z 1170.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol-

d₄) δ 8.53 (s, 1H), 8.29 - 8.25 (m, 1H), 8.16 (d, J = 9.2 Hz, 1H), 8.12 (s, 1H), 7.70 - 7.60 (m, 2H), 7.55 (td, J = 7.4, 3.1 Hz, 1H), 7.50 (s, 1H), 7.36 (d, J = 2.1 Hz, 1H), 7.34 (s, 1H), 7.24 (dd, J = 8.2, 6.7 Hz, 4H), 7.16 (d, J = 10.0 Hz, 1H), 6.79 (d, J = 9.9 Hz, 1H), 4.94 (t, J = 7.6 Hz, 2H), 4.79 (dd, J = 8.2, 5.2 Hz, 3H), 4.49 (s, 1H), 4.47 - 4.41 (m, 1H), 4.34 - 4.27 (m, 1H), 4.15 (d, J = 8.8 Hz, 1H), 4.09 (d, J = 7.1 Hz, 3H), 3.93 (d, J = 13.2 Hz, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.57 (d, J = 13.5 Hz, 2H), 3.51 (s, 0H), 3.47 (dt, J = 3.3, 1.7 Hz, 2H), 3.43 (s, 1H), 2.99 (s, 0H), 2.91 (d, J = 7.8 Hz, 2H), 2.87 - 2.82 (m, 1H), 2.81 - 2.73 (m, 1H), 2.36 (s, 4H), 2.34 (s, 0H), 2.24 (s, 2H), 2.04 - 1.91 (m, 0H), 1.33 - 1.26 (m, 1H), 1.17 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H). ^{19}F NMR (377 MHz, Methanol-d₄) δ -77.39, -77.51, -77.71, -96.88 (d, J = 59.6 Hz), -115.03, -130.01.

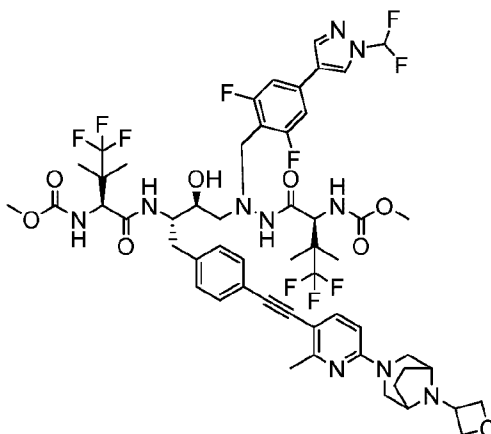
**EXAMPLE 154**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-

16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((4-methyl-6-(8-(oxetan-3-yl)-3,8-

diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-
2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (154).

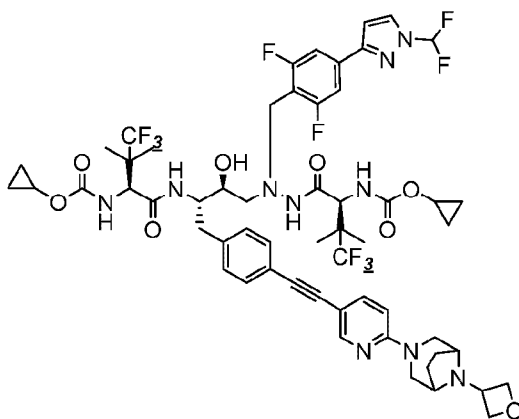
Intermediates: **P7**, **A3**, and **S46**. MS (ESI) m/z 1169.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 1H), 8.20 (s, 1H), 8.14 (s, 1H), 8.11 (s, 1H), 7.64 (s, 0H), 7.50 (s, 1H), 7.34 (d, J = 7.3 Hz, 2H), 7.24 (t, J = 7.8 Hz, 4H), 7.11 (d, J = 9.9 Hz, 1H), 6.78 (s, 1H), 6.77 (s, 0H), 4.96 (t, J = 7.6 Hz, 2H), 4.50 (s, 1H), 4.44 (d, J = 9.7 Hz, 1H), 4.36 - 4.27 (m, 3H), 4.12 (d, J = 10.0 Hz, 4H), 3.94 (d, J = 13.2 Hz, 1H), 3.70 (s, 2H), 3.68 (s, 3H), 3.66 (s, 3H), 3.38 (s, 1H), 3.34 (s, 3H), 2.94 - 2.73 (m, 4H), 2.44 (s, 3H), 2.27 - 2.17 (m, 2H), 2.07 (d, J = 8.6 Hz, 2H), 1.29 (t, J = 7.4 Hz, 0H), 1.20 - 1.10 (m, 10H), 1.03 (s, 3H). ^{19}F NMR (376 MHz, Methanol- d_4) δ -77.35, -77.62, -77.67, -96.90 (d, J = 59.9 Hz), -115.01.



EXAMPLE 155

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-methyl-6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (155).

Intermediates: **P7**, **A3**, and **S45**. MS (ESI) m/z 1169.7 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 1H), 8.12 (s, 2H), 7.64 (s, 0H), 7.53 (d, J = 8.6 Hz, 1H), 7.49 (s, 1H), 7.37 - 7.28 (m, 3H), 7.23 (dd, J = 15.6, 8.1 Hz, 5H), 4.44 (s, 1H), 4.30 (s, 2H), 4.12 (d, J = 12.6 Hz, 3H), 3.94 (d, J = 13.1 Hz, 1H), 3.68 (s, 4H), 3.66 (s, 4H), 2.90 (d, J = 8.2 Hz, 2H), 2.79 (d, J = 9.9 Hz, 1H), 2.53 (s, 4H), 2.03 (s, 0H), 1.98 (s, 1H), 1.28 (d, J = 7.2 Hz, 3H), 1.17 (s, 5H), 1.15 (s, 4H), 1.12 (s, 4H), 1.03 (s, 4H). ^{19}F NMR (376 MHz, Methanol- d_4) δ -77.36, -77.48, -77.68, -96.91 (d, J = 59.7 Hz).

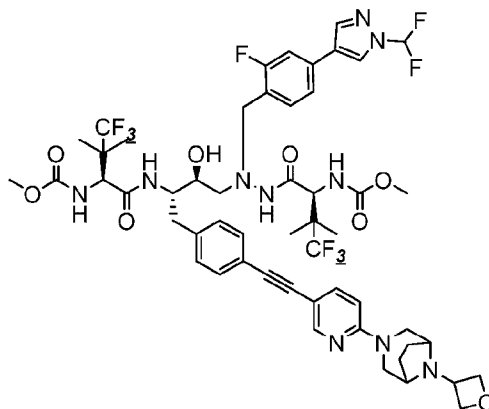
**EXAMPLE 156**

Cyclopropyl ((2S)-1-(2-((2S,3S)-3-((S)-2-((cyclopropoxycarbonyl)amino)-4,4,4-trifluoro-3,3-dimethylbutanamido)-2-hydroxy-4-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)phenyl)butyl)-2-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)hydrazinyl)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)carbamate (156).

Intermediates: **P4**, **A6**, and **S3**. MS (ESI) m/z 1208.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.30 (dd, J = 2.3, 0.7 Hz, 1H), 8.21 (d, J = 9.4 Hz, 1H), 8.11 (d, J = 2.7 Hz, 1H), 7.81 - 7.63 (m, 1H), 7.53 (s, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.42 - 7.29 (m, 3H), 7.23 (d, J = 8.0 Hz, 3H), 6.94 (d, J = 2.8 Hz, 1H), 6.85 (t, J = 8.7 Hz, 2H), 5.05 - 4.90 (m, 3H), 4.48 (d, J = 10.0 Hz,

1H), 4.34 (t, J = 12.0 Hz, 3H), 4.24 - 3.84 (m, 7H), 3.75 (s, 1H), 3.01 - 2.66 (m, 5H), 2.22 (dd, J = 12.2, 6.4 Hz, 2H), 2.03 (s, 32H), 1.29 (s, 1H), 1.19 - 1.07 (m, 10H), 1.03 (s, 3H), 1.00 - 0.50 (m, 8H).

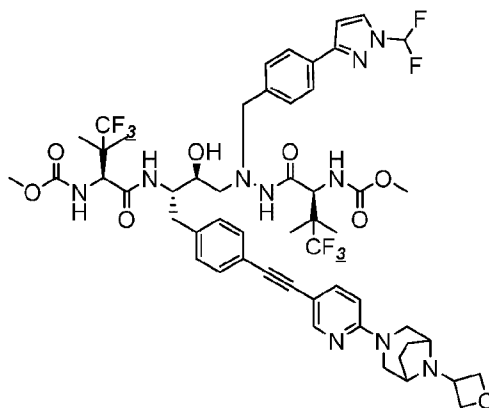
5



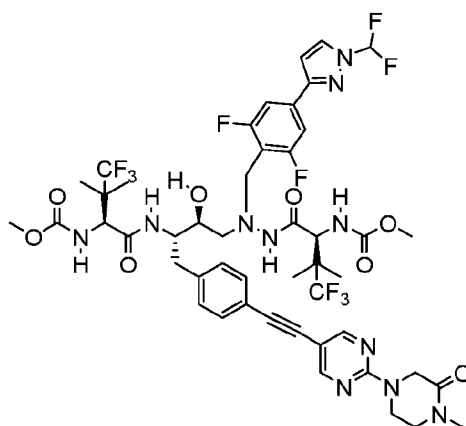
EXAMPLE 157

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (157).

Intermediates: **P8**, **A3**, and **S3**. MS (ESI) m/z 1138.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.43 (s, 1H), 8.28 - 8.25 (m, 1H), 8.07 (s, 1H), 7.68 (dd, J = 8.9, 2.3 Hz, 1H), 7.66 - 7.57 (m, 1H), 7.57 - 7.45 (m, 1H), 7.41 - 7.27 (m, 6H), 7.20 (d, J = 8.2 Hz, 2H), 6.90 - 6.81 (m, 1H), 4.94 (dd, J = 8.1, 7.0 Hz, 3H), 4.81 (dd, J = 8.1, 4.9 Hz, 3H), 4.53 (d, J = 6.3 Hz, 1H), 4.45 - 4.21 (m, 5H), 4.14 (dd, J = 4.7, 2.4 Hz, 4H), 4.08 - 3.83 (m, 3H), 3.70 (d, J = 24.6 Hz, 2H), 3.60 (s, 3H), 3.38 (dd, J = 14.1, 1.7 Hz, 3H), 3.29 (p, J = 1.6 Hz, 6H), 2.93 - 2.66 (m, 5H), 2.28 - 2.02 (m, 3H), 1.11 (d, J = 14.3 Hz, 7H), 1.04 (s, 4H), 0.93 (s, 4H).

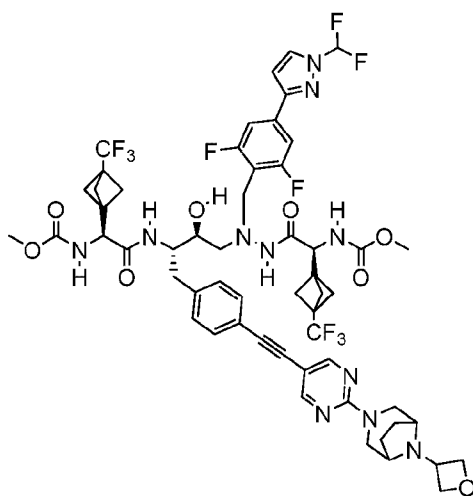
**EXAMPLE 158**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (158). Intermediates: **P6**, **A3**, and **S3**. MS (ESI) m/z 1120.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.20 (dd, J = 2.3, 0.7 Hz, 1H), 8.16 - 7.99 (m, 2H), 7.84 - 7.73 (m, 2H), 7.71 - 7.37 (m, 4H), 7.37 - 7.26 (m, 3H), 7.26 - 7.10 (m, 2H), 6.86 (d, J = 2.7 Hz, 1H), 6.69 (dd, J = 9.0, 0.8 Hz, 1H), 4.76 (t, J = 6.4 Hz, 2H), 4.58 (t, J = 5.8 Hz, 3H), 4.39 (s, 1H), 4.25 (s, 1H), 4.01 (d, J = 13.1 Hz, 1H), 3.89 (dt, J = 13.1, 4.1 Hz, 4H), 3.85 - 3.74 (m, 1H), 3.60 (s, 3H), 3.12 (dd, J = 12.0, 2.2 Hz, 3H), 2.98 - 2.60 (m, 4H), 1.96 - 1.86 (m, 3H), 1.69 (d, J = 7.8 Hz, 2H), 1.11 (d, J = 9.3 Hz, 7H), 1.02 (s, 3H), 1.00 - 0.76 (m, 4H).



EXAMPLE 159

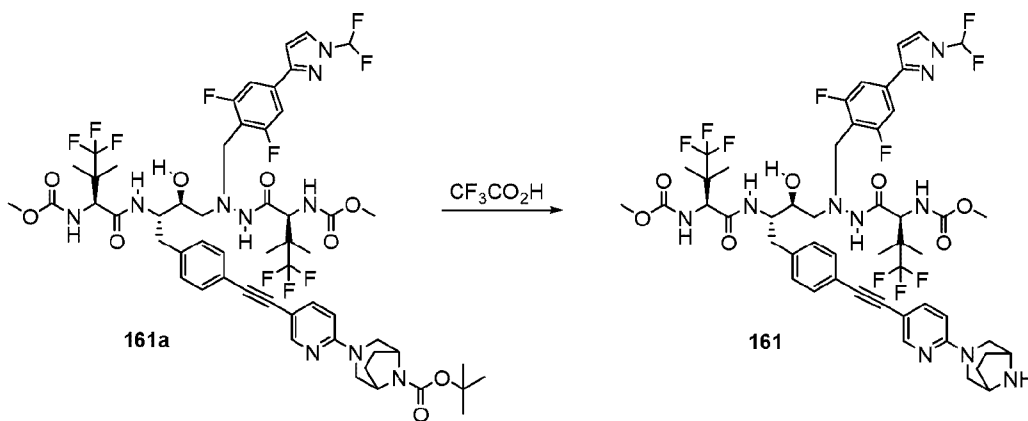
methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-(4-methyl-3-oxopiperazin-1-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (159). Intermediates: **P4**, **A3**, and **S58**. MS (ESI) m/z 1102.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.50 (s, 2H), 8.20 (d, J = 9.5 Hz, 1H), 8.12 (s, 1H), 7.55 (t, J = 61.0 Hz, 1H), 7.46 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 7.7 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 6.95 (s, 1H), 4.44 (s, 1H), 4.40 (s, 2H), 4.31 (s, 1H), 4.15 (d, J = 15.7 Hz, 4H), 3.95 (d, J = 12.9 Hz, 1H), 3.75 (s, 2H), 3.70 (s, 3H), 3.67 (s, 3H), 3.50 (s, 2H), 3.03 (d, J = 2.8 Hz, 3H), 2.90 (t, J = 12.3 Hz, 2H), 2.80 (d, J = 10.7 Hz, 1H), 1.17 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.04 (s, 3H).

**EXAMPLE 160**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-8-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5,14-bis(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)-2-oxa-4,7,11,12-tetraazatetradecan-14-yl)carbamate (160). Intermediates: **P4**, **A8**, and **S7**. MS (ESI) m/z 1205.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.51 (s, 2H), 8.09 (d, J = 2.7 Hz, 1H), 7.52 (t, J = 60.0, 59.5 Hz, 1H), 7.48 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 2.7 Hz, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.81 (dd, J = 8.3, 5.1 Hz, 2H), 4.76 (s, 1H), 4.33 - 4.23 (m, 1H), 4.18 - 4.12 (m, 3H), 4.08 (d, J = 18.2 Hz, 2H), 4.03 (d, J = 13.5 Hz, 1H), 3.75 (d, J = 9.3 Hz, 1H), 3.66 (s, 3H), 3.64 (s, 3H), 3.46 (d, J = 14.4 Hz, 2H),

3.04 - 2.85 (m, 3H), 2.79 (d, J = 12.7 Hz, 1H), 2.20 (dd, J = 8.9, 3.9 Hz, 2H), 2.01 (dd, J = 12.2, 6.9 Hz, 2H), 1.86 - 1.65 (m, 12H).

EXAMPLE 161

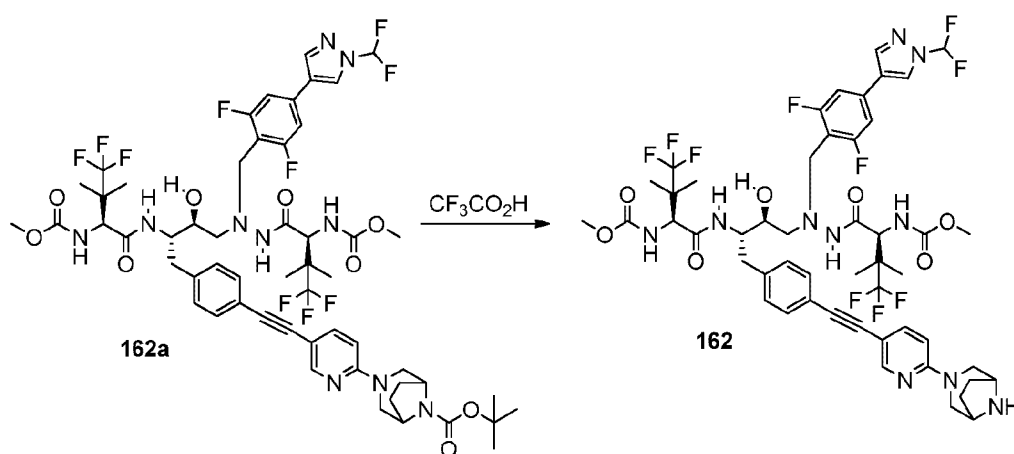


5

tert-butyl 3-(5-((4-((2S,3S)-4-(1-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-2-((S)-4,4,4-trifluoro-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)hydrazinyl)-3-hydroxy-2-((S)-4,4,4-trifluoro-2-((methoxycarbonyl) amino)-3,3-dimethylbutanamido)butyl)phenyl)ethynyl)pyridin-2-yl)-3,8-diazabicyclo[3.2.1] octane-8-carboxylate (161a). MS (ESI) m/z 1200.0 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.27 - 8.14 (m, 2H), 8.11 (d, J = 2.7 Hz, 1H), 7.84 (d, J = 9.0 Hz, 1H), 7.53 (t, J = 59.7 Hz, 2H), 7.45 (d, J = 8.2 Hz, 3H), 7.35 (d, J = 7.9 Hz, 3H), 7.24 (d, J = 8.0 Hz, 3H), 7.15 (d, J = 9.5 Hz, 1H), 7.08 (d, J = 9.3 Hz, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.82 (d, J = 10.0 Hz, 1H), 4.44 (d, J = 11.9 Hz, 4H), 4.30 (d, J = 10.0 Hz, 1H), 4.14 (d, J = 13.3 Hz, 3H), 4.02 - 3.87 (m, 4H), 3.67 (d, J = 10.7 Hz, 10H), 3.28 - 3.18 (m, 3H), 3.03 - 2.85 (m, 4H), 2.82 - 2.69 (m, 1H), 2.00 (dd, J = 9.0, 4.0 Hz, 3H), 1.81 (d, J = 7.7 Hz, 3H), 1.49 (s, 9H), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H).

Methyl ((5S,8S,9S,14S)-8-(4-((6-(3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate 2,2,2-trifluoroacetate (161). A solution of **161a** (57.8 mg, 0.040 mmol) and trifluoroacetic acid (0.150 ml, 1.96 mmol) in DCM (2 mL) was stirred at room temperature. After 3 h, the reaction mixture was concentrated under reduced pressure and the residue was purified by HPLC and the product lyophilized to afford **161**. MS (ESI) m/z 1200.0 [M+H]⁺. ¹H NMR (400 MHz,

Methanol-d₄) δ 8.32 - 8.26 (m, 1H), 8.18 (d, J = 9.4 Hz, 1H), 8.11 (d, J = 2.7 Hz, 1H), 7.71 - 7.64 (m, 1H), 7.71 - 7.36 (m, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 10.0 Hz, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.82 (t, J = 9.9 Hz, 2H), 4.44 (d, J = 9.9 Hz, 1H), 4.36 - 4.22 (m, 4H), 4.16 (d, J = 28.1 Hz, 4H), 3.94 (d, J = 13.2 Hz, 1H), 3.67 (d, J = 11.1 Hz, 8H), 3.26 - 3.17 (m, 3H), 2.99 - 2.69 (m, 5H), 2.19 - 1.96 (m, 5H), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H).

EXAMPLE 162

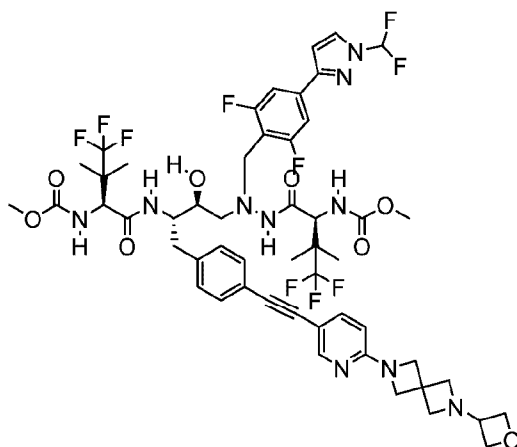
10

Synthesis of tert-butyl 3-(5-((4-((2S,3S)-4-(1-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-2-((S)-4,4,4-trifluoro-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)hydrazinyl)-3-hydroxy-2-((S)-4,4,4-trifluoro-2-((methoxycarbonyl)amino)-3,3-dimethylbutanamido)butyl)phenyl)ethynyl)pyridin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (162a). Intermediates: **P7**, **A3**, and **S16**. MS (ESI) m/z 1199.4 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.53 (d, J = 0.7 Hz, 1H), 8.21 - 8.09 (m, 3H), 7.89 (dd, J = 9.4, 2.2 Hz, 1H), 7.69 - 7.32 (m, 2H), 7.35 (s, 1H), 7.24 (dd, J = 8.4, 2.4 Hz, 4H), 7.14 (d, J = 9.4 Hz, 2H), 4.43 (d, J = 4.2 Hz, 3H), 4.36 - 4.23 (m, 1H), 4.23 - 4.00 (m, 2H), 3.97 - 3.82 (m, 3H), 3.67 (d, J = 9.7 Hz, 5H), 3.28 (d, J = 9.6 Hz, 2H), 3.00 - 2.70 (m, 4H), 2.08 - 1.91 (m, 2H), 1.82 (t, J = 6.9 Hz, 2H), 1.49 (s, 9H), 1.23 - 1.08 (m, 9H), 1.03 (s, 3H).

20

Methyl ((5S,8S,9S,14S)-8-(4-((6-(3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-

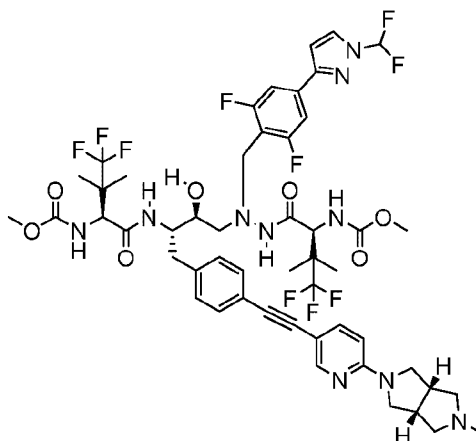
methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate. The title compound **162** was prepared according to the method presented for the synthesis of compound **161** but instead utilizing **162a**. MS (ESI) m/z 1099.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.45 (s, 1H), 8.18 (d, J = 2.3 Hz, 1H), 8.08 (d, J = 9.4 Hz, 1H), 8.03 (s, 1H), 7.63 - 7.55 (m, 1H), 7.41 (s, 1H), 7.29 - 7.20 (m, 2H), 7.14 (dd, J = 14.9, 8.2 Hz, 4H), 6.73 (t, J = 9.6 Hz, 2H), 4.34 (d, J = 9.7 Hz, 1H), 4.28 - 4.13 (m, 4H), 4.13 - 3.91 (m, 4H), 3.83 (d, J = 13.1 Hz, 1H), 3.58 (d, J = 10.5 Hz, 7H), 3.14 (d, J = 13.5 Hz, 2H), 2.75 (dd, J = 47.8, 9.1 Hz, 4H), 2.12 - 1.85 (m, 3H), 1.16 - 0.97 (m, 9H), 0.94 (s, 3H).



EXAMPLE 163

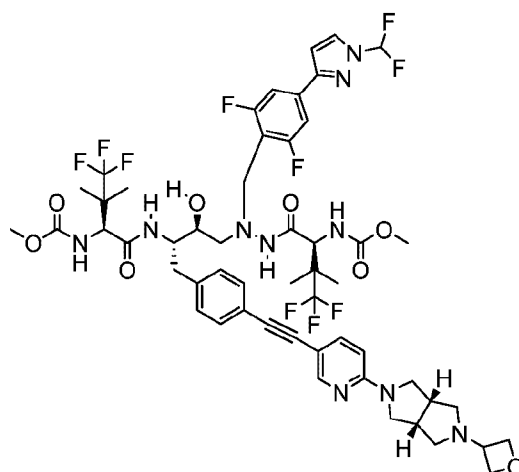
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(6-(oxetan-3-yl)-2,6-diazaspiro[3.3]heptan-2-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (163**).**

Intermediates: **P4**, **A3**, and **S17**. MS (ESI) m/z 1141.7 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.17 - 8.03 (m, 2H), 8.01 (d, J = 2.7 Hz, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.44 (t, J = 59.8 Hz, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 7.8 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 9.8 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.72 (d, J = 9.9 Hz, 1H), 6.50 (d, J = 8.9 Hz, 1H), 4.90 - 4.82 (m, 1H), 4.49 - 4.34 (m, 6H), 4.28 (s, 4H), 4.21 (d, J = 10.0 Hz, 1H), 4.05 (d, J = 13.0 Hz, 2H), 3.85 (d, J = 13.2 Hz, 1H), 3.64 (s, 2H), 3.59 (s, 3H), 3.57 (s, 3H), 2.88 - 2.74 (m, 3H), 2.74 - 2.63 (m, 1H), 1.06 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H).

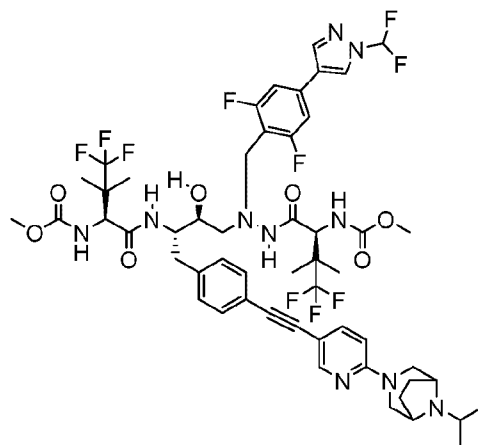


EXAMPLE 164

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(((6-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (164). Intermediates: **P4**, **A3**, and **S18**. MS (ESI) m/z 1114.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.19 - 8.05 (m, 2H), 8.01 (d, J = 2.7 Hz, 1H), 7.61 (dd, J = 8.9, 2.2 Hz, 1H), 7.44 (t, J = 59.8 Hz, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 9.9 Hz, 1H), 6.85 (d, J = 2.7 Hz, 1H), 6.72 (d, J = 10.0 Hz, 1H), 6.64 (d, J = 8.9 Hz, 1H), 4.35 (d, J = 9.8 Hz, 1H), 4.21 (d, J = 10.0 Hz, 1H), 4.05 (d, J = 12.6 Hz, 2H), 3.85 (d, J = 13.1 Hz, 2H), 3.65 (s, 1H), 3.58 (d, J = 10.7 Hz, 6H), 3.36 (d, J = 14.9 Hz, 2H), 2.84 (dd, J = 18.9, 9.2 Hz, 5H), 2.70 (d, J = 10.2 Hz, 1H), 1.06 (d, J = 6.3 Hz, 6H), 1.02 (s, 3H), 0.93 (s, 3H).

**EXAMPLE 165**

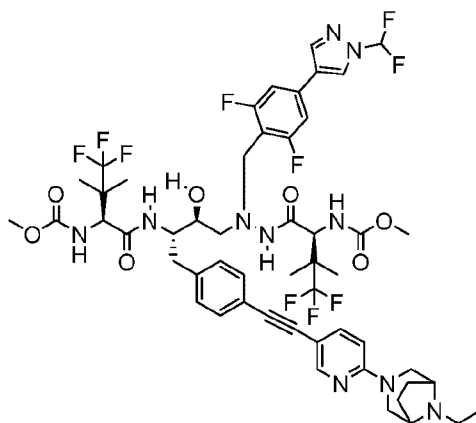
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(((6-((3aR,6aS)-5-(oxetan-3-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (165). Intermediates: **P4**, **A3**, and **S19**. MS (ESI) m/z 1156.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.09 (d, $J = 2.3$ Hz, 2H), 8.01 (d, $J = 2.7$ Hz, 1H), 7.72 (dd, $J = 8.9, 2.2$ Hz, 1H), 7.44 (t, $J = 59.8$ Hz, 1H), 7.36 (d, $J = 8.2$ Hz, 2H), 7.25 (d, $J = 7.9$ Hz, 2H), 7.14 (d, $J = 8.0$ Hz, 2H), 7.05 (d, $J = 9.9$ Hz, 1H), 6.85 (d, $J = 2.7$ Hz, 1H), 6.81 - 6.67 (m, 2H), 4.63 (dd, $J = 8.3, 5.1$ Hz, 2H), 4.46 - 4.30 (m, 2H), 4.21 (d, $J = 10.0$ Hz, 1H), 4.05 (d, $J = 13.3$ Hz, 2H), 3.85 (d, $J = 13.2$ Hz, 1H), 3.64 (d, $J = 4.3$ Hz, 6H), 3.59 (s, 3H), 3.57 (s, 3H), 3.32 (s, 3H), 2.87 - 2.62 (m, 4H), 1.06 (d, $J = 6.2$ Hz, 6H), 1.02 (s, 3H), 0.93 (s, 3H).



EXAMPLE 166

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-8-(((6-(8-isopropyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (166).

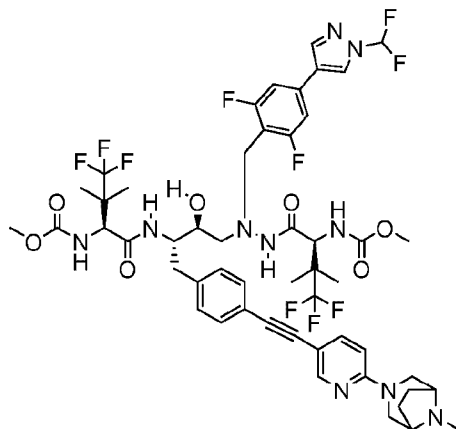
Intermediates: **P7**, **A3**, and **S22**. MS (ESI) m/z 1142.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.44 (d, $J = 0.7$ Hz, 1H), 8.20 (s, 1H), 8.07 (d, $J = 9.5$ Hz, 1H), 8.06 - 8.02 (m, 1H), 7.67 - 7.50 (m, 1H), 7.50 - 7.43 (m, 0H), 7.41 (s, 0H), 7.29 - 7.20 (m, 2H), 7.14 (dd, $J = 13.7, 8.3$ Hz, 3H), 6.73 (dd, $J = 18.5, 9.6$ Hz, 1H), 4.34 (t, $J = 5.2$ Hz, 3H), 4.30 - 4.15 (m, 3H), 4.13 - 3.94 (m, 3H), 3.84 (d, $J = 13.2$ Hz, 1H), 3.58 (d, $J = 10.5$ Hz, 6H), 3.17 (d, $J = 2.4$ Hz, 1H), 2.91 - 2.64 (m, 3H), 2.14 (d, $J = 11.4$ Hz, 2H), 1.95 (d, $J = 8.6$ Hz, 1H), 1.37 (d, $J = 6.4$ Hz, 6H), 1.12 - 0.97 (m, 9H), 0.94 (s, 3H).

**EXAMPLE 167**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-8-(4-(((6-(8-ethyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (167). Intermediates: **P7**, **A3**, and **S21**.

MS (ESI) m/z 1128.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.44 (d, $J = 0.7$ Hz, 1H), 8.19 (d, $J = 2.2$ Hz, 1H), 8.06 (d, $J = 21.7$ Hz, 2H), 7.63 - 7.53 (m, 1H), 7.41 (s, 1H), 7.28 - 7.21 (m, 2H), 7.14 (dd, $J = 13.9, 8.2$ Hz, 4H), 6.73 (dd, $J = 18.8, 9.5$ Hz, 2H), 4.42 - 4.30 (m, 1H), 4.30 - 4.18 (m, 3H), 4.13 (d, $J = 4.3$ Hz, 2H), 4.02 (d, $J = 12.6$ Hz, 2H), 3.84 (d, $J = 13.2$ Hz,

1H), 3.58 (d, J = 10.5 Hz, 7H), 3.09 (q, J = 7.3 Hz, 2H), 2.92 - 2.72 (m, 3H), 2.72 - 2.61 (m, 1H), 2.24 - 2.13 (m, 2H), 1.96 (d, J = 8.7 Hz, 2H), 1.32 (t, J = 7.3 Hz, 3H), 1.11 - 0.98 (m, 9H), 0.94 (s, 3H).

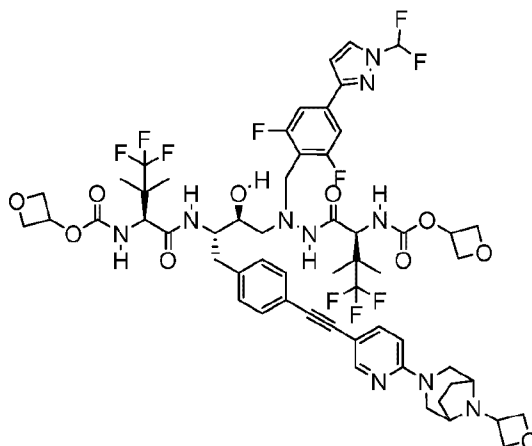


5

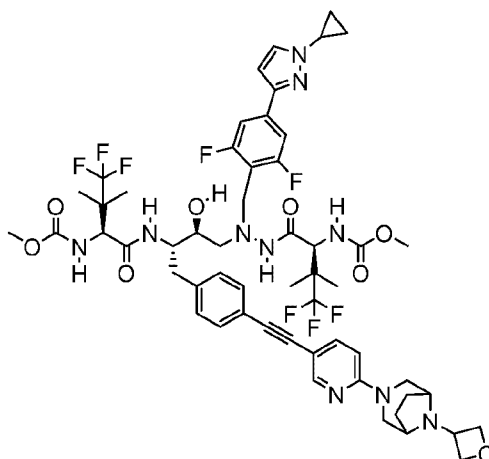
EXAMPLE 168

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (168).

Intermediates: **P7**, **A3**, and **S20**. MS (ESI) m/z 1113.4 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.45 (d, J = 0.7 Hz, 1H), 8.24 - 8.16 (m, 1H), 8.08 (d, J = 9.3 Hz, 1H), 8.03 (s, 1H), 7.63 - 7.54 (m, 1H), 7.41 (s, 1H), 7.28 - 7.21 (m, 2H), 7.14 (dd, J = 14.5, 8.2 Hz, 5H), 6.74 (dd, J = 15.5, 9.4 Hz, 2H), 4.34 (d, J = 9.9 Hz, 1H), 4.24 (dd, J = 17.7, 11.9 Hz, 3H), 4.02 (d, J = 13.4 Hz, 4H), 3.83 (d, J = 13.2 Hz, 1H), 3.58 (d, J = 10.4 Hz, 7H), 3.16 (s, 1H), 3.06 - 2.96 (m, 0H), 2.85 - 2.58 (m, 6H), 2.31 - 2.13 (m, 2H), 2.05 - 1.89 (m, 2H), 1.13 - 0.96 (m, 9H), 0.94 (s, 3H).

**EXAMPLE 169**

oxetan-3-yl ((2S)-1-(2-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-2-
 ((2S,3S)-2-hydroxy-4-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-
 5 yl)ethynyl)phenyl)-3-((S)-4,4,4-trifluoro-3,3-dimethyl-2-(((oxetan-3-
 yloxy)carbonyl)amino)butanamido)butyl)hydrazinyl)-4,4,4-trifluoro-3,3-dimethyl-1-
 oxobutan-2-yl)carbamate (169). Intermediates: **P4**, **A4**, and **S3**. MS (ESI) m/z 1239.3 [M+H]
 +. ¹H NMR (400 MHz, Methanol-d₄) δ 8.13 (d, J = 2.3 Hz, 1H), 8.09 (d, J = 9.4 Hz, 1H), 8.02
 (d, J = 2.8 Hz, 1H), 7.52 (dd, J = 8.9, 2.4 Hz, 1H), 7.45 (t, J = 59.9 Hz, 1H), 7.37 (d, J = 8.2 Hz,
 10 2H), 7.21 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.61 (d, J = 9.0
 Hz, 1H), 5.29 (dp, J = 17.2, 5.7 Hz, 2H), 4.76 - 4.73 (m, 4H), 4.67 (t, J = 6.4 Hz, 2H), 4.56 (ddd,
 J = 10.3, 7.3, 5.4 Hz, 2H), 4.52 - 4.42 (m, 4H), 4.32 (s, 1H), 4.20 (s, 1H), 4.11 - 4.00 (m, 2H),
 3.90 - 3.76 (m, 3H), 3.77 - 3.60 (m, 2H), 3.08 - 2.97 (m, 2H), 2.89 - 2.75 (m, 3H), 2.73 - 2.63
 (m, 1H), 1.90 - 1.81 (m, 2H), 1.68 - 1.56 (m, 2H), 1.09 (s, 3H), 1.07 (s, 3H), 1.03 (s, 3H), 0.95
 15 (s, 3H).



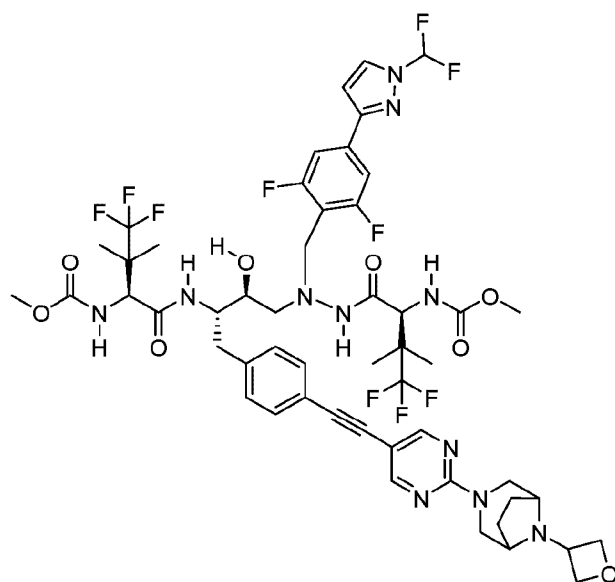
EXAMPLE 170

Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-

16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (170).

Intermediates: **P13**, **A3**, and **S3**. MS (ESI) m/z 1146.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol-

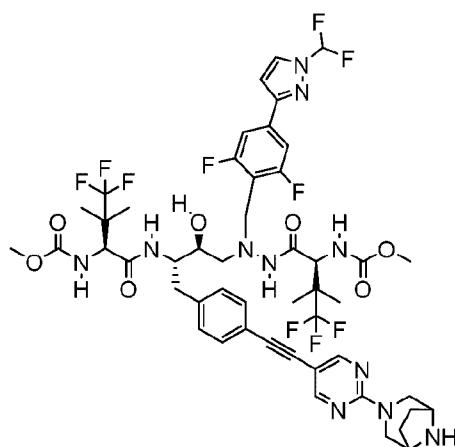
d_4) δ 8.29 (dd, $J = 2.3, 0.8$ Hz, 1H), 8.18 (d, $J = 9.2$ Hz, 1H), 7.70 (td, $J = 4.9, 4.4, 2.3$ Hz, 2H),
 7.39 - 7.27 (m, 4H), 7.22 (d, $J = 8.1$ Hz, 2H), 7.16 (d, $J = 9.9$ Hz, 1H), 6.86 (d, $J = 8.9$ Hz, 1H),
 6.80 (d, $J = 9.9$ Hz, 1H), 6.64 (d, $J = 2.4$ Hz, 1H), 4.96 (dd, $J = 8.2, 7.0$ Hz, 2H), 4.81 (dd, $J =$
 8.3, 5.1 Hz, 2H), 4.46 - 4.41 (m, 1H), 4.39 - 4.33 (m, 1H), 4.31 (d, $J = 10.0$ Hz, 1H), 4.19 - 4.07
 (m, 4H), 3.93 (d, $J = 13.2$ Hz, 1H), 3.76 - 3.70 (m, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.40 - 3.34
 (m, 2H), 2.95 - 2.70 (m, 4H), 2.30 - 2.18 (m, 2H), 2.12 - 2.01 (m, 2H), 1.22 - 1.04 (m, 13H),
 1.02 (s, 3H).

**EXAMPLE 171**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((2-(8-(oxetan-3-yl)-3,8-

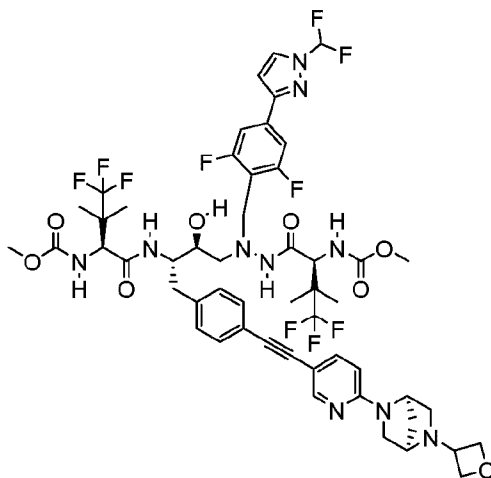
5 diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (171).
 Intermediates: **P4**, **A3**, and **S7**. MS (ESI) m/z 1156.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.43 (s, 2H), 8.08 (d, $J = 9.4$ Hz, 1H), 8.01 (d, $J = 2.8$ Hz, 1H), 7.44 (d, $J = 59.8$ Hz, 1H), 7.35 (d, $J = 8.2$ Hz, 2H), 7.25 (d, $J = 7.9$ Hz, 2H), 7.14 (d, $J = 8.1$ Hz, 2H), 7.03 (d, $J = 9.9$ Hz, 1H), 6.84 (d, $J = 2.7$ Hz, 1H), 6.71 (d, $J = 9.9$ Hz, 1H), 4.87 (t, $J = 7.6$ Hz, 2H), 4.72 (dd, $J = 8.2$, 4.9 Hz, 2H), 4.67 (s, 1H), 4.42 - 4.29 (m, 1H), 4.25 - 4.18 (m, 1H), 4.11 - 3.98 (m, 4H), 3.85 (d, $J = 13.1$ Hz, 1H), 3.69 - 3.62 (m, 2H), 3.59 (s, 3H), 3.57 (s, 3H), 3.41 - 3.28 (m, 2H), 2.87 - 2.75 (m, 3H), 2.68 (dd, $J = 12.6, 9.1$ Hz, 1H), 2.18 - 2.06 (m, 2H), 1.95 - 1.83 (m, 2H), 1.07 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H).

15

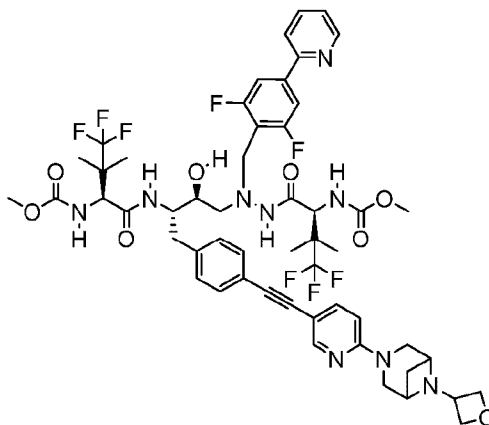
**EXAMPLE 172**

Methyl ((5S,8S,9S,14S)-8-(4-((2-(3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (172).

Intermediates: **P4**, **A3**, and **S36**. MS (ESI) m/z 1100.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.41 (s, 2H), 8.08 (d, $J = 9.2$ Hz, 1H), 8.01 (d, $J = 2.7$ Hz, 1H), 7.44 (d, $J = 59.8$ Hz, 1H), 7.36 (d, $J = 8.2$ Hz, 2H), 7.25 (d, $J = 7.9$ Hz, 2H), 7.14 (d, $J = 8.1$ Hz, 2H), 7.03 (d, $J = 8.5$ Hz, 1H), 6.84 (d, $J = 2.8$ Hz, 1H), 6.70 (d, $J = 10.2$ Hz, 1H), 4.66 - 4.57 (m, 2H), 4.35 (d, $J = 9.6$ Hz, 1H), 4.26 - 4.17 (m, 1H), 4.12 - 3.96 (m, 5H), 3.85 (d, $J = 13.2$ Hz, 1H), 3.69 - 3.62 (m, 2H), 3.59 (s, 3H), 3.57 (s, 3H), 3.25 (s, 1H), 2.87 - 2.61 (m, 4H), 2.05 - 1.96 (m, 2H), 1.90 - 1.82 (m, 2H), 1.07 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H).

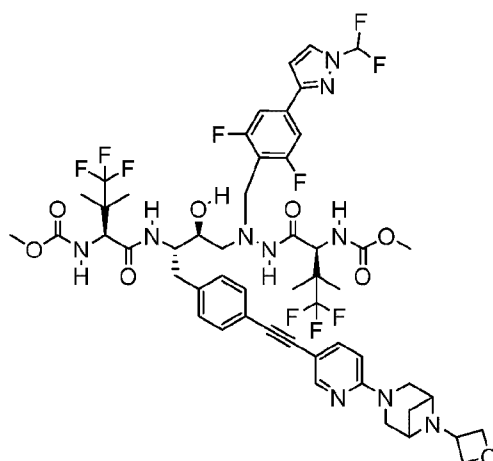


- 7.68 (m, 1H), 7.53 (t, J = 59.6 Hz, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 9.9 Hz, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.80 (d, J = 9.9 Hz, 1H), 6.71 - 6.61 (m, 1H), 5.05 (s, 1H), 4.99 - 4.93 (m, 1H), 4.70 (dd, J = 8.4, 4.5 Hz, 1H), 4.64 - 4.53 (m, 2H), 4.51 (s, 1H), 4.44 (d, J = 9.8 Hz, 1H), 4.30 (d, J = 10.0 Hz, 1H), 4.18 - 4.10 (m, 2H),
 5 3.94 (d, J = 13.1 Hz, 1H), 3.79 (dd, J = 11.9, 2.2 Hz, 1H), 3.76 - 3.70 (m, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 2.94 - 2.73 (m, 4H), 2.33 (s, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H).



EXAMPLE 175

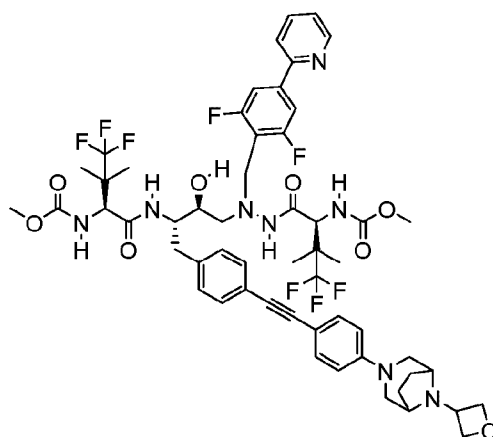
- 10 **Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-((6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (175).** Intermediates: **P28**, **A3**, and **S4**. MS (ESI) m/z 1102.4 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.66 (d, J = 5.0 Hz, 1H), 8.33
 15 (d, J = 2.2 Hz, 1H), 8.14 (d, J = 9.4 Hz, 1H), 8.03 - 7.88 (m, 2H), 7.74 (dd, J = 8.7, 2.3 Hz, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.46 (t, J = 6.1 Hz, 1H), 7.34 (d, J = 7.8 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.11 (d, J = 9.4 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 4.97 (s, 3H), 4.62 (dd, J = 8.1, 4.1 Hz, 2H), 4.44 (d, J = 8.2 Hz, 1H), 4.34 - 4.26 (m, 1H), 4.26 - 4.07 (m, 4H), 3.98 (d, J = 13.1 Hz, 2H), 3.79 - 3.71 (m, 1H), 3.70 (s, 3H), 3.64 (s, 3H), 2.99 - 2.85 (m, 3H), 2.84 - 2.74 (m, 1H),
 20 2.11 (d, J = 11.2 Hz, 1H), 1.16 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H), 1.03 (s, 3H).

**EXAMPLE 176**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(6-(oxetan-3-yl)-3,6-

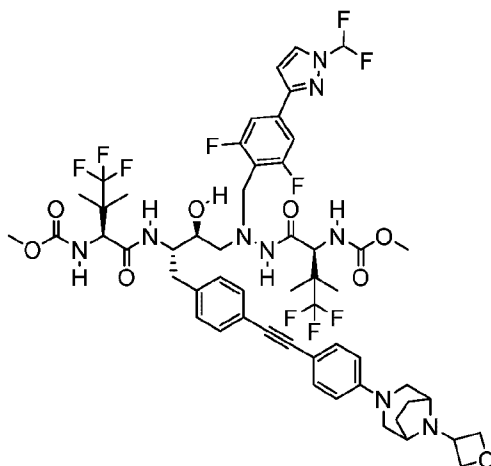
5 diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (176).

Intermediates: **P4**, **A3**, and **S4**. MS (ESI) m/z 1141.8 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.33 (d, $J = 2.1$ Hz, 1H), 8.14 (d, $J = 9.3$ Hz, 1H), 8.10 (d, $J = 2.8$ Hz, 1H), 7.74 (dd, $J = 8.8, 2.2$ Hz, 1H), 7.53 (t, $J = 59.8$ Hz, 1H), 7.45 (d, $J = 8.2$ Hz, 2H), 7.34 (d, $J = 7.9$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 10.3$ Hz, 1H), 6.93 (d, $J = 2.8$ Hz, 1H), 6.78 (d, $J = 8.8$ Hz, 2H), 5.07 - 4.91 (m, 3H), 4.61 (dd, $J = 8.2, 4.1$ Hz, 2H), 4.44 (d, $J = 9.9$ Hz, 1H), 4.31 (d, $J = 10.0$ Hz, 1H), 4.23 - 4.06 (m, 3H), 3.95 (d, $J = 13.3$ Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 2.95 - 2.70 (m, 4H), 2.10 (d, $J = 11.1$ Hz, 1H), 1.16 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H).



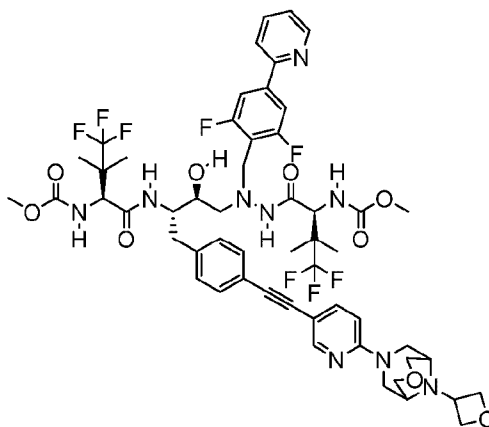
EXAMPLE 177

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((4-((8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)phenyl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (177). Intermediates: **P28**, **A3**, and **S3**. MS (ESI) m/z 1115.9 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.69 - 8.60 (m, 1H), 8.18 (d, J = 9.3 Hz, 1H), 7.94 (q, J = 7.9 Hz, 2H), 7.60 (d, J = 8.6 Hz, 2H), 7.44 (t, J = 5.7 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 10.7 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 10.0 Hz, 1H), 5.01 - 4.92 (m, 3H), 4.84 - 4.76 (m, 2H), 4.44 (d, J = 9.9 Hz, 1H), 4.31 (d, J = 10.0 Hz, 1H), 4.23 - 4.10 (m, 4H), 3.97 (d, J = 13.1 Hz, 1H), 3.85 (d, J = 13.0 Hz, 2H), 3.79 - 3.72 (m, 1H), 3.69 (s, 3H), 3.63 (s, 3H), 2.93 - 2.84 (m, 3H), 2.83 - 2.75 (m, 1H), 2.21 (q, J = 11.1, 10.5 Hz, 4H), 1.27 (d, J = 5.7 Hz, 1H), 1.16 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H). ¹⁹F NMR (377 MHz, Methanol-d₄) δ -77.39, -77.73, -77.85, -114.65.

**EXAMPLE 178**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((4-((8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)phenyl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (178). Intermediates: **P4**, **A3**, and **S3**. MS (ESI) m/z 1154.4 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.07 (d, J = 9.4 Hz, 1H), 8.01 (d, J = 2.7 Hz, 1H), 7.44 (t, 1H), 7.36 (d, J = 8.2 Hz, 2H),

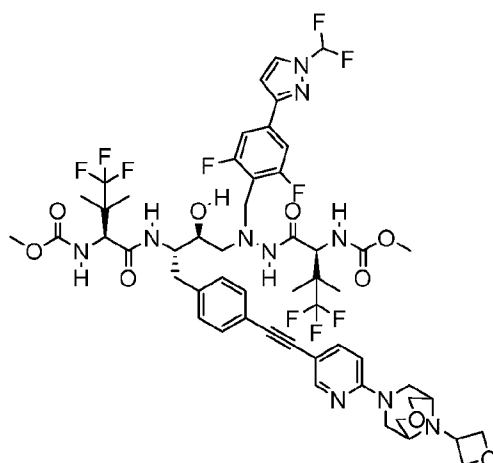
7.30 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 6.89 - 6.82 (m, 3H), 4.86 (t, J = 7.5 Hz, 2H), 4.72 - 4.64 (m, 2H), 4.35 (d, J = 6.4 Hz, 1H), 4.25 - 4.16 (m, 1H), 4.11 - 3.95 (m, 3H), 3.85 (d, J = 12.5 Hz, 1H), 3.80 - 3.70 (m, 1H), 3.68 - 3.62 (m, 1H), 3.60 (s, 3H), 3.57 (s, 3H), 2.85 - 2.63 (m, 4H), 2.18 - 1.99 (m, 4H), 1.22 - 1.18 (m, 2H), 1.07 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H). ¹⁹F NMR (377 MHz, Methanol-d₄) δ -77.40 , -77.49 , -77.73 , -96.96 (dd, J = 60.0, 18.7 Hz), -114.92 .



10

EXAMPLE 179

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(9-(oxetan-3-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (179). Intermediates: **P28**, **A3**, and **S1**. MS (ESI) m/z 1133.1 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.66 (d, J = 4.8 Hz, 1H), 8.21 - 8.10 (m, 2H), 8.02 - 7.82 (m, 3H), 7.60 (d, J = 8.6 Hz, 2H), 7.46 (t, J = 6.3 Hz, 1H), 7.36 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 9.4 Hz, 1H), 4.82 - 4.76 (m, 2H), 4.66 - 4.58 (m, 2H), 4.51 - 4.41 (m, 1H), 4.35 - 4.27 (m, 1H), 4.23 - 4.13 (m, 2H), 4.13 - 3.89 (m, 7H), 3.78 - 3.72 (m, 2H), 3.69 (s, 3H), 3.68 - 3.65 (m, 3H), 3.63 (s, 3H), 3.18 - 3.08 (m, 2H), 3.00 - 2.84 (m, 3H), 2.84 - 2.74 (m, 1H), 1.16 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H). ¹⁹F NMR (377 MHz, Methanol-d₄) δ -77.37 , -77.71 , -77.99 , -114.58 .

**EXAMPLE 180**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-

16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(((6-(9-(oxetan-3-yl)-3-oxa-7,9-

5 diazabicyclo[3.3.1]nonan-7-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-
2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (180).

Intermediates: **P4**, **A3**, and **S1**. MS (ESI) m/z 1171.8 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.20 - 8.13 (m, 2H), 8.10 (d, $J = 2.7$ Hz, 1H), 7.87 (d, $J = 8.7$ Hz, 1H), 7.60 (t, $J = 59.8$ Hz, 1H), 7.45 (d, $J = 8.2$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.24 (d, $J = 8.1$ Hz, 2H), 7.15 (d, $J = 9.5$ Hz, 1H), 6.93 (d, $J = 2.7$ Hz, 1H), 4.80 - 4.75 (m, 1H), 4.74 - 4.67 (m, 1H), 4.62 (t, $J = 5.7$ Hz, 2H), 4.46 - 4.40 (m, 1H), 4.32 - 4.25 (m, 1H), 4.21 - 4.00 (m, 6H), 3.99 - 3.89 (m, 3H), 3.78 - 3.71 (m, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.12 (d, $J = 4.9$ Hz, 2H), 2.98 - 2.72 (m, 4H), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.38, -77.71, -77.85, -96.97 (dd, $J = 59.7, 19.1$ Hz), -114.93.

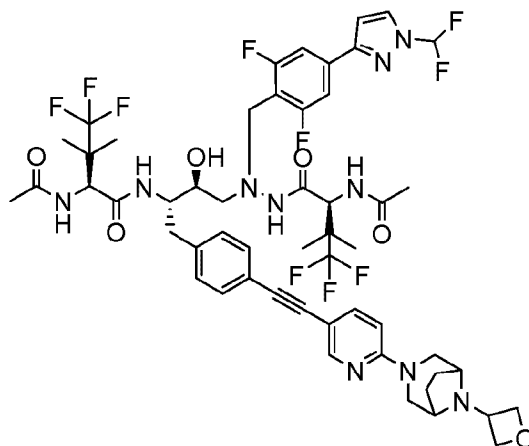
15

20

trifluoro-2-methylpropan-2-yl)-3-oxa-5,8,9,13-tetraazaheptadecan-15-yl)carbamate (181c)

The title compound **181c** was prepared according to the method presented for the synthesis of compound **133** but instead utilizing **181b** and **S3**. MS (ESI) m/z 1239.9 $[M+H]^+$.

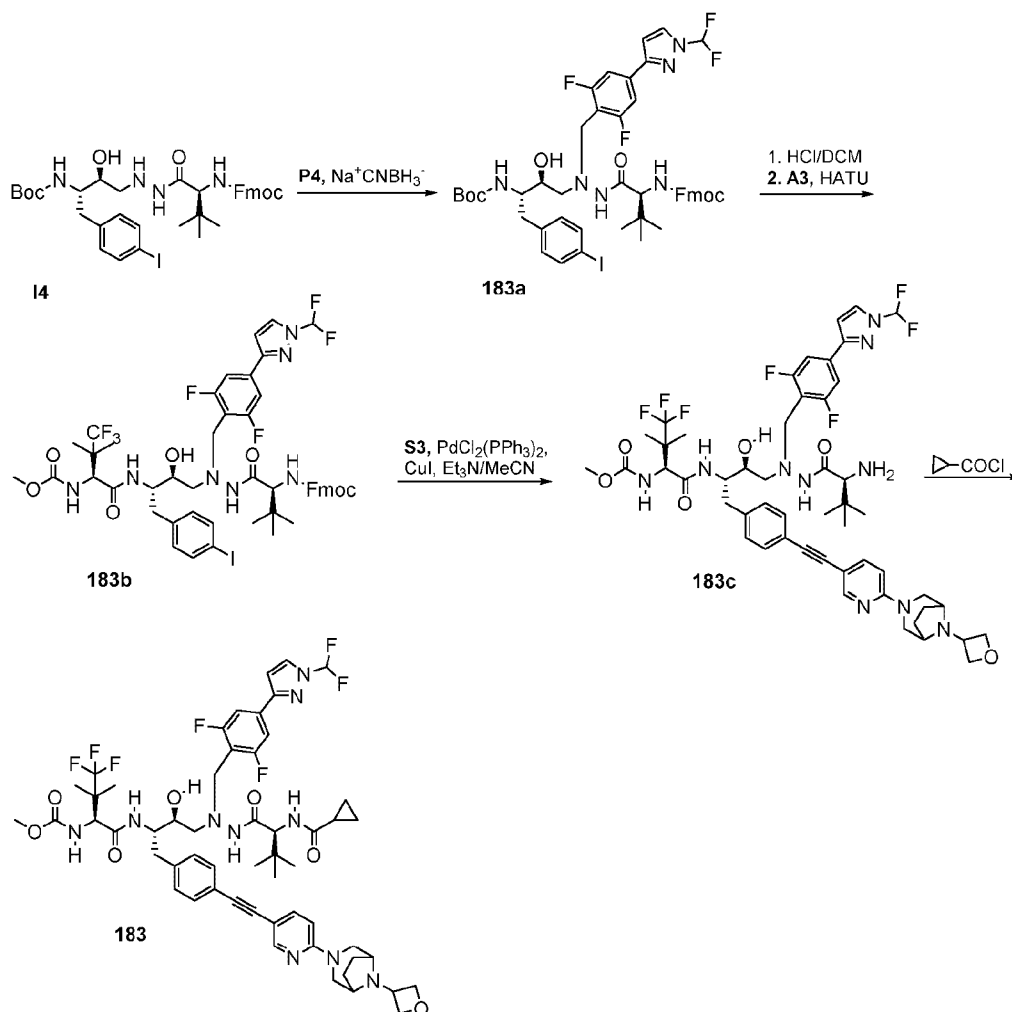
(2S)-N-((2S,3S)-4-(1-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-2-((S)-4,4,4-trifluoro-3,3-dimethyl-2-propionamidobutanoyl)hydrazinyl)-3-hydroxy-1-(4-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)phenyl)butan-2-yl)-4,4,4-trifluoro-3,3-dimethyl-2-propionamidobutanamide (**181**). To a solution of **181c** (355 mg, 0.29 mmol) in DCM (10 mL) was added trifluoroacetic acid (2 mL), the mixture was stirred and after 18 h, the reaction mixture was concentrated under reduced pressure and the crude material was dissolved in DMF (3 mL) and HATU (35.28 mg, 0.16 mmol), N, N-diisopropylethylamine (0.13 mL, 0.74 mmol) was added followed by propionic acid (0.01 mL, 0.16 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was purified by HPLC to afford **181**. MS (ESI) m/z 1152.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.20 (dd, J = 2.3, 0.7 Hz, 1H), 8.11 (d, J = 2.7 Hz, 1H), 7.74 - 7.37 (m, 4H), 7.37 - 7.23 (m, 2H), 7.23 - 7.12 (m, 2H), 6.95 (d, J = 2.8 Hz, 1H), 6.70 (dd, J = 9.1, 0.8 Hz, 1H), 4.83 - 4.71 (m, 3H), 4.66 (s, 1H), 4.59 (dd, J = 6.3, 5.4 Hz, 3H), 4.23 - 4.13 (m, 2H), 4.00 - 3.84 (m, 4H), 3.84 - 3.70 (m, 1H), 3.13 (dd, J = 12.0, 2.2 Hz, 3H), 2.95 - 2.71 (m, 4H), 2.21 (ttd, J = 7.5, 5.0, 2.3 Hz, 4H), 1.97 - 1.90 (m, 2H), 1.70 (d, J = 7.8 Hz, 2H), 1.18 (d, J = 9.3 Hz, 7H), 1.16 - 1.00 (m, 13H).

**EXAMPLE 182**

(2S)-2-acetamido-N-((2S,3S)-4-(2-((S)-2-acetamido-4,4,4-trifluoro-3,3-dimethylbutanoyl)-1-

(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)hydrazinyl)-3-hydroxy-1-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)phenyl)butan-2-yl)-4,4,4-trifluoro-3,3-dimethylbutanamide (182). The title compound **182** was prepared according to the method presented for the synthesis of compound **181** but instead utilizing

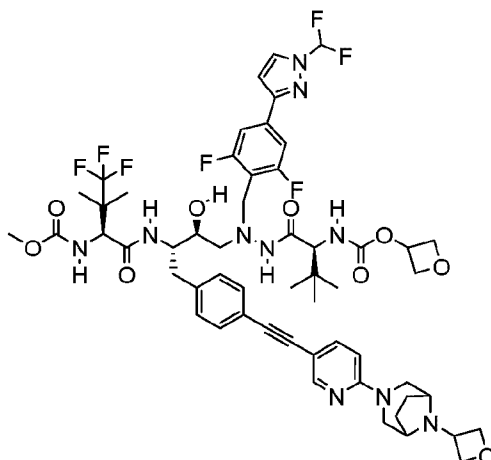
- 5 Intermediates: **P4**, **A1**, **S3** and acetic acid. MS (ESI) m/z 1123.9 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.18 (dd, J = 2.3, 0.7 Hz, 1H), 8.09 (d, J = 2.7 Hz, 1H), 7.72 - 7.35 (m, 4H), 7.35 - 7.24 (m, 2H), 7.20 - 7.11 (m, 2H), 6.94 (d, J = 2.8 Hz, 1H), 6.69 (dd, J = 9.0, 0.8 Hz, 1H), 4.76 (dd, J = 12.8, 6.4 Hz, 3H), 4.63 (d, J = 1.4 Hz, 1H), 4.57 (dd, J = 6.3, 5.4 Hz, 3H), 4.15 (d, J = 13.4 Hz, 2H), 3.98 - 3.65 (m, 5H), 3.11 (dd, J = 12.0, 2.2 Hz, 3H), 2.98 - 2.67 (m, 4H), 2.13 (d, J = 10.3 Hz, 0H), 1.98 - 1.83 (m, 9H), 1.68 (d, J = 7.8 Hz, 2H), 1.17 (d, J = 6.2 Hz, 6H), 1.12 (s, 3H), 1.04 (s, 3H), 0.88 (d, J = 6.7 Hz, 0H).
- 10

EXAMPLE 183

- 5 **Synthesis of (9H-fluoren-9-yl)methyl ((S)-1-(2-((2S,3S)-3-((tert-butoxycarbonyl)amino)-2-hydroxy-4-(4-iodophenyl)butyl)-2-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (183a)** The title compound **183a** was prepared according to the method presented for the synthesis of compound **133a** but instead utilizing **I4** and **P4**. MS (ESI) m/z 999.3 $[\text{M}+\text{H}]^+$.
- 10 **Synthesis of (9H-fluoren-9-yl)methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-8-(4-iodobenzyl)-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (183b)** The title compound **183b** was prepared according to the method presented

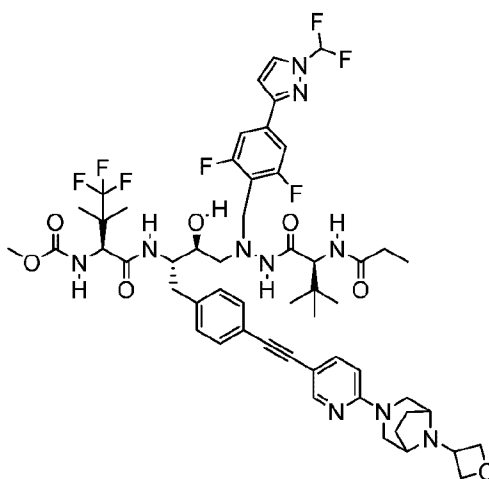
for the synthesis of compound **133b** but instead utilizing **4a** and **A3**. MS (ESI) m/z 1124.6 $[M+H]^+$.

- Synthesis of methyl ((2S)-1-(((2S,3S)-4-(2-((S)-2-amino-3,3-dimethylbutanoyl)-1-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)hydrazinyl)-3-hydroxy-1-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)phenyl)butan-2-yl)amino)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)carbamate (183c)** The title compound **183c** was prepared according to the method presented for the synthesis of compound **133** but instead utilizing **183b** and **S3**. MS (ESI) m/z 1043.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.29 (dd, J = 2.3, 0.7 Hz, 1H), 8.14 - 8.07 (m, 2H), 7.75 - 7.65 (m, 1H), 7.53 (d, J = 59.8 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.25 - 7.18 (m, 2H), 6.94 (d, J = 2.8 Hz, 1H), 6.86 (dd, J = 9.0, 0.9 Hz, 1H), 6.78 (d, J = 9.9 Hz, 1H), 4.99 - 4.93 (m, 3H), 4.84 (d, J = 5.2 Hz, 1H), 4.82 (d, J = 5.0 Hz, 1H), 4.54 (s, 1H), 4.42 - 4.30 (m, 3H), 4.26 - 4.06 (m, 5H), 3.81 (t, J = 6.6 Hz, 1H), 3.65 (s, 1H), 3.45 - 3.36 (m, 3H), 2.97 - 2.76 (m, 4H), 2.28 - 2.19 (m, 2H), 2.11 - 2.03 (m, 2H), 1.09 (s, 3H), 1.06 (s, 3H), 0.97 (s, 9H).
- Synthesis of methyl ((2S)-1-(((2S,3S)-4-(2-((S)-2-(cyclopropanecarboxamido)-3,3-dimethylbutanoyl)-1-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)hydrazinyl)-3-hydroxy-1-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)phenyl)butan-2-yl)amino)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)carbamate (183)** To a solution of **183c** (45 mg, 0.33 mmol) in DCM (1 mL) was added Et_3N (0.03 mL, 0.23 mmol) at 5 °C, cyclopropanecarbonyl chloride (3.54 μ L, 0.39 mmol) was added and the mixture was stirred for 10 min, then diluted with MeOH, concentrated under reduced pressure and the residue was purified by HPLC to afford **183**. MS (ESI) m/z 1111.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.35 - 8.26 (m, 1H), 8.18 (d, J = 9.4 Hz, 1H), 8.11 (d, J = 2.7 Hz, 1H), 7.91 (d, J = 8.9 Hz, 1H), 7.71 (dd, J = 8.8, 2.3 Hz, 1H), 7.53 (t, J = 59.7 Hz, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 6.94 (d, J = 2.8 Hz, 1H), 6.87 (d, J = 8.9 Hz, 1H), 6.78 (d, J = 9.9 Hz, 1H), 5.03 - 4.94 (m, 2H), 4.84 - 4.77 (m, 3H), 4.44 (d, J = 9.9 Hz, 1H), 4.41 - 4.31 (m, 1H), 4.21 - 4.06 (m, 5H), 3.96 (d, J = 13.1 Hz, 1H), 3.81 - 3.72 (m, 1H), 3.70 (s, 3H), 3.39 (s, 1H), 2.91 (d, J = 7.7 Hz, 2H), 2.88 - 2.73 (m, 2H), 2.29 - 2.19 (m, 2H), 2.15 - 2.04 (m, 2H), 1.74 - 1.67 (m, 1H), 1.31 (t, J = 7.5 Hz, 1H), 1.14 (s, 3H), 1.10 (s, 3H), 0.89 (s, 9H), 0.75 (dd, J = 8.2, 3.6 Hz, 2H).



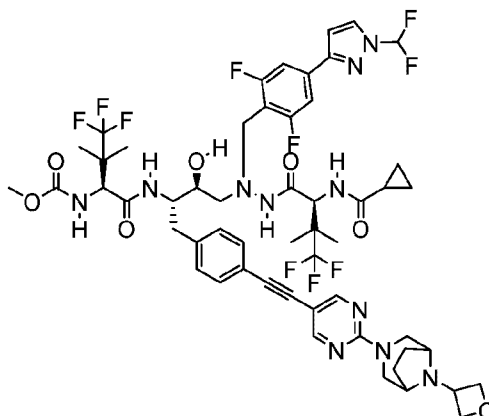
EXAMPLE 184

methyl ((2S)-1-(((2S,3S)-4-(1-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-
 2-((S)-3,3-dimethyl-2-(((oxetan-3-yloxy)carbonyl)amino)butanoyl)hydrazinyl)-3-hydroxy-
 1-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-
 yl)ethynyl)phenyl)butan-2-yl)amino)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-
 yl)carbamate. Intermediates: **P4**, **A3**, **S3** and 4-nitrophenyl oxetan-3-yl carbonate. MS (ESI)
 m/z 1143.6 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.25 - 8.19 (m, 1H), 8.09 (d, J = 9.3
 Hz, 1H), 8.01 (d, J = 2.7 Hz, 1H), 7.65 - 7.59 (m, 1H), 7.44 (t, J = 59.7 Hz, 1H), 7.36 (d, J = 8.1
 Hz, 2H), 7.23 (d, J = 7.9 Hz, 3H), 7.13 (d, J = 8.0 Hz, 3H), 6.85 (d, J = 2.7 Hz, 1H), 6.77 (d, J =
 8.9 Hz, 1H), 6.71 (d, J = 9.6 Hz, 1H), 4.87 (t, J = 7.6 Hz, 3H), 4.76 - 4.68 (m, 2H), 4.51 (dt, J =
 23.0, 6.4 Hz, 2H), 4.31 - 4.22 (m, 2H), 4.12 - 3.99 (m, 5H), 3.87 (d, J = 13.1 Hz, 1H), 3.70 - 3.62
 (m, 2H), 3.59 (s, 3H), 3.30 (s, 1H), 2.89 - 2.60 (m, 5H), 2.18 - 2.10 (m, 2H), 2.03 - 1.95 (m, 2H),
 1.24 - 1.17 (m, 2H), 1.05 (s, 3H), 1.01 (s, 3H), 0.78 (s, 9H).



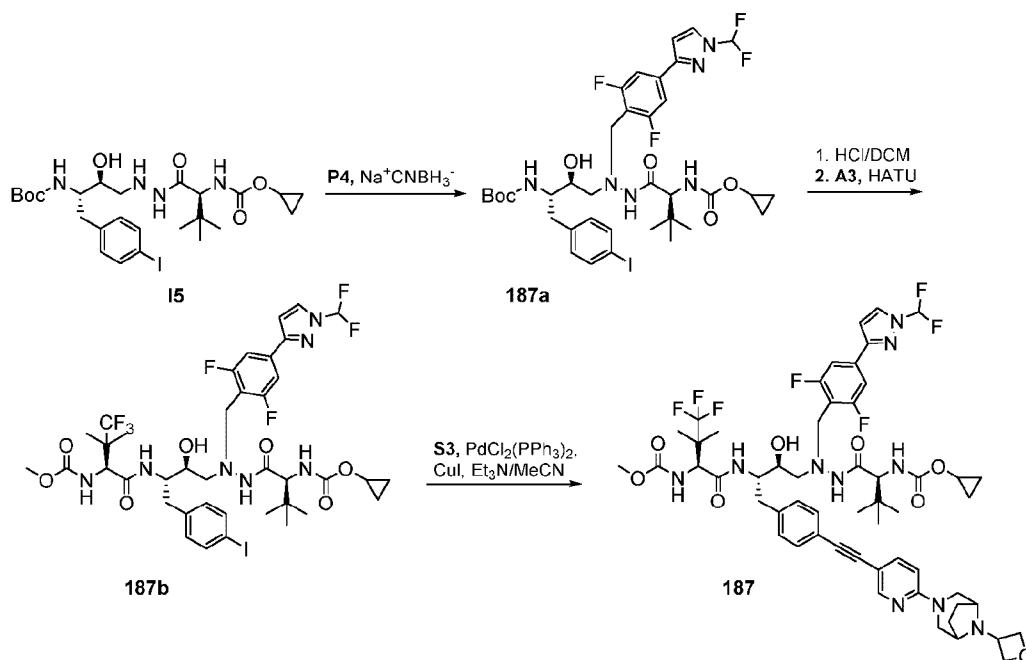
EXAMPLE 185

Methyl ((2S)-1-(((2S,3S)-4-(1-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-2-((S)-3,3-dimethyl-2-propionamidobutanoyl)hydrazinyl)-3-hydroxy-1-(4-(((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)phenyl)butan-2-yl)amino)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)carbamate. Intermediates: **P4**, **A3**, **S3** and propionyl chloride MS (ESI) m/z 1099.6 $M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.22 - 8.18 (m, 1H), 8.08 (d, J = 9.2 Hz, 1H), 8.01 (d, J = 2.7 Hz, 1H), 7.61 (dd, J = 8.9, 2.3 Hz, 1H), 7.56 (d, J = 9.2 Hz, 1H), 7.43 (d, J = 59.9 Hz, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.77 (d, J = 8.9 Hz, 1H), 6.69 (d, J = 9.9 Hz, 1H), 4.87 (dd, J = 8.1, 6.9 Hz, 2H), 4.73 - 4.69 (m, 2H), 4.36 - 4.31 (m, 1H), 4.30 - 4.19 (m, 3H), 4.09 - 4.02 (m, 4H), 4.01 - 3.96 (m, 1H), 3.86 (d, J = 13.2 Hz, 1H), 3.68 - 3.62 (m, 1H), 3.59 (s, 3H), 3.31 - 3.24 (m, 2H), 2.84 - 2.64 (m, 3H), 2.18 - 2.07 (m, 2H), 2.03 - 1.94 (m, 2H), 1.04 (s, 3H), 1.03 - 0.97 (m, 6H), 0.77 (s, 9H).

**EXAMPLE 186**

Methyl ((2S)-1-(((2S,3S)-4-(2-((S)-2-(cyclopropanecarboxamido)-4,4,4-trifluoro-3,3-dimethylbutanoyl)-1-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)hydrazinyl)-3-hydroxy-1-(4-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)phenyl)butan-2-yl)amino)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)carbamate (186). Intermediates: **P4**, **A3**, **S7** and cyclopropanecarboxylic acid.

MS (ESI) m/z 1167.0 $M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 2H), 8.22 (d, $J = 9.6$ Hz, 1H), 8.14 (d, $J = 9.4$ Hz, 1H), 8.09 (d, $J = 2.7$ Hz, 1H), 7.52 (t, $J = 59.9$ Hz, 1H), 7.45 (d, $J = 8.2$ Hz, 2H), 7.34 (d, $J = 7.9$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 6.92 (d, $J = 2.8$ Hz, 1H), 6.75 (d, $J = 9.9$ Hz, 1H), 4.96 (t, $J = 7.6$ Hz, 2H), 4.82 - 4.77 (m, 2H), 4.75 (s, 1H), 4.65 (d, $J = 9.7$ Hz, 1H), 4.43 (d, $J = 9.9$ Hz, 1H), 4.23 - 4.07 (m, 4H), 3.92 (d, $J = 13.0$ Hz, 1H), 3.74 (d, $J = 8.6$ Hz, 1H), 3.69 (s, 3H), 3.45 (d, $J = 14.5$ Hz, 2H), 2.97 - 2.82 (m, 3H), 2.81 - 2.69 (m, 1H), 2.27 - 2.10 (m, 2H), 2.03 - 1.89 (m, 2H), 1.74 - 1.63 (m, 1H), 1.19 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.97 - 0.88 (m, 1H), 0.87 - 0.70 (m, 3H).

EXAMPLE 187

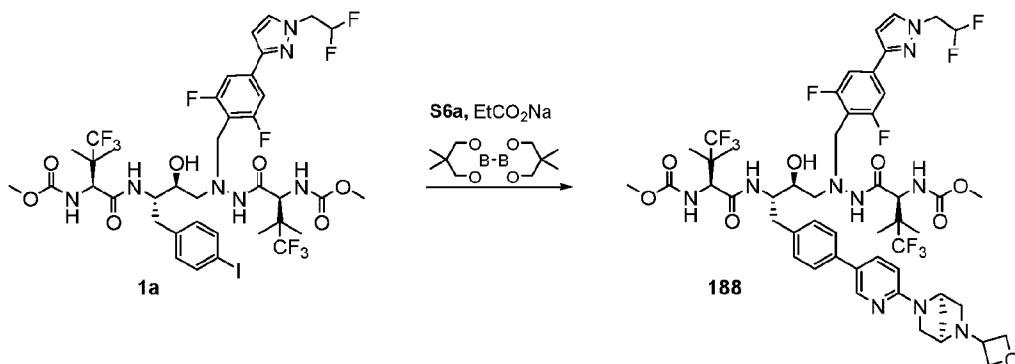
Synthesis of cyclopropyl ((S)-1-(2-((2S,3S)-3-((tert-butoxycarbonyl)amino)-2-hydroxy-4-(4-iodophenyl)butyl)-2-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-

5 difluorobenzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**187a**). The title compound **187a** was prepared according to the method presented for the synthesis of compound **133a** but instead utilizing **I5** and **P4**. MS (ESI) m/z 861.1 $[M+H]^+$.

Synthesis of cyclopropyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-8-(4-iodobenzyl)-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (**187b**). The title compound **187b** was prepared according to the method presented for the synthesis of compound **133b** but instead utilizing **5a**. MS (ESI) m/z 986.5 $[M+H]^+$.

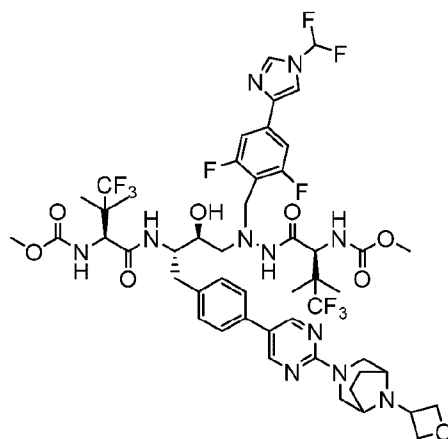
Synthesis of cyclopropyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (**187**). The title compound **187** was prepared according to the method presented for the synthesis of compound **133** but instead utilizing **187b** and **S3**. MS (ESI) m/z 1127.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.33 - 8.25 (m, 1H), 8.18 (d, J = 9.3 Hz, 1H), 8.10 (d, J = 2.7 Hz, 1H), 7.74 - 7.66 (m, 1H), 7.53 (d, J = 59.7 Hz, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.22

(d, J = 8.1 Hz, 2H), 6.93 (d, J = 2.7 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 6.80 (d, J = 9.9 Hz, 1H), 4.96 (t, J = 7.5 Hz, 2H), 4.81 (dd, J = 8.2, 5.2 Hz, 2H), 4.44 (d, J = 10.0 Hz, 1H), 4.35 (d, J = 13.6 Hz, 2H), 4.23 - 4.06 (m, 4H), 4.03 - 3.92 (m, 2H), 3.82 - 3.74 (m, 1H), 3.69 (s, 3H), 3.40 - 3.33 (m, 2H), 2.97 - 2.73 (m, 3H), 2.31 - 2.18 (m, 2H), 2.11 - 2.04 (m, 2H), 1.16 - 1.12 (m, 3H), 1.10 (s, 3H), 0.85 (s, 9H), 0.68 - 0.58 (m, 4H).

EXAMPLE 188

Synthesis of methyl ((5S,8S,9S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(6-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (188) A suspension of **S6a** (59.8 mg, 0.167 mmol), bis(neopentylglycolato)diboron (38 mg, 0.168 mmol), potassium propionate (44.5 mg, 0.397 mmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (2.8 mg, 0.004 mmol) in 2-MeTHF (1 mL) was degassed with argon for 15 min, then heated at 90 °C overnight. Cooled to room temperature, then added 1M Potassium Phosphate in H_2O (0.39 ml) and degassed for 5 min. Added $\text{Pd}(\text{tBu}_2\text{PPh})_2\text{Cl}_2$ (4.5 mg, 0.007 mmol) and **1a** (100 mg, 0.1 mmol) in 2-Me THF (1 mL) and degassed an additional 5 min. Heated at 65 °C. The reaction mixture was cooled to room temperature. Diluted with EtOAc and washed with brine. The separated organic layer was dried over Na_2SO_4 and concentrated under vacuum, the residue was purified by HPLC and the product was lyophilized to afford **188**. MS (ESI) m/z 1131.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Methanol- d_4) δ 8.19 (s, 1H), 8.10 (d, J = 9.3 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 2.5 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 9.9 Hz, 1H), 6.82 (d, J = 9.0 Hz, 1H), 6.76 (d, J = 9.8 Hz, 1H), 6.65 (d, J = 2.5 Hz, 1H), 6.32 - 5.96 (m, 1H), 4.96 (s, 1H), 4.61 (dd, J = 8.2, 4.7 Hz, 1H), 4.58 - 4.49 (m, 3H), 4.45 (dd, J = 14.2, 4.8 Hz, 1H), 4.37 (s, 1H), 4.21 (d, J = 9.9 Hz, 1H), 4.04 (d, J = 13.0 Hz, 2H), 3.84 (d, J = 13.2 Hz, 1H), 3.74 (d, J = 11.9

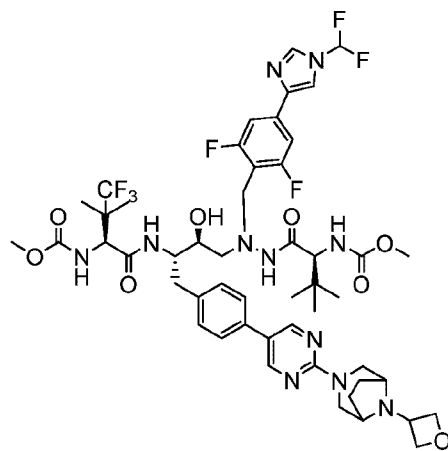
Hz, 1H), 3.67 (d, J = 11.5 Hz, 2H), 3.54 (s, 4H), 3.47 (s, 3H), 2.92 - 2.73 (m, 4H), 2.73 - 2.62 (m, 1H), 2.24 (s, 2H), 1.05 (d, J = 4.5 Hz, 7H), 1.01 (s, 3H), 0.92 (s, 3H).



EXAMPLE 189

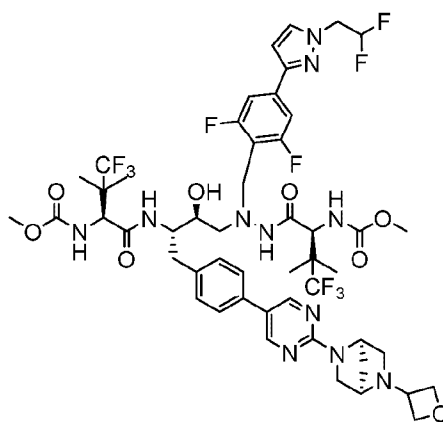
- 5 **Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-imidazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (189).**

Intermediates: **I2**, **P1** and **S7a**. MS (ESI) m/z 1132.9 [M+H]⁺. ¹H NMR (400 MHz, Methanol-
 10 d₄) δ 8.65 (s, 2H), 8.19 (d, J = 7.9 Hz, 2H), 8.02 (s, 1H), 7.59 (t, J = 60.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 2H), 7.17 (d, J = 10.0 Hz, 1H), 6.88 (d, J = 9.9 Hz, 0H), 4.96 (t, J = 7.6 Hz, 2H), 4.83 (dd, J = 8.3, 5.3 Hz, 2H), 4.47 (d, J = 7.2 Hz, 2H), 4.39 - 4.23 (m, 1H), 4.13 (d, J = 13.3 Hz, 5H), 3.93 (d, J = 13.3 Hz, 1H), 3.75 (s, 1H), 3.65 (s, 3H), 3.56 (s, 3H), 3.47 (d, J = 14.5 Hz, 2H), 3.03 - 2.73 (m, 4H), 2.29 - 2.11 (m, 2H), 2.01 (d, J = 9.1 Hz, 2H), 1.14 (d, J = 5.2 Hz, 6H), 1.10 (s,
 15 3H), 1.02 (s, 3H).



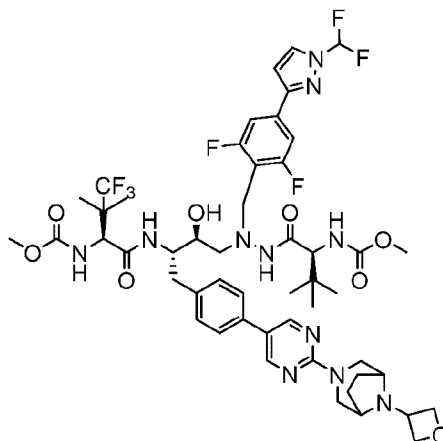
EXAMPLE 190

- methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-imidazol-4-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(4-(2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (190).** Intermediates: **I3**, **P1** and **S7a**. MS (ESI) m/z 1079.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.56 (s, 2H), 8.20 - 8.03 (m, 2H), 7.92 (d, J = 1.3 Hz, 1H), 7.49 (t, J = 59.9 Hz, 1H), 7.31 (dd, J = 9.9, 8.2 Hz, 4H), 7.22 (d, J = 7.8 Hz, 2H), 6.79 (d, J = 10.0 Hz, 0H), 4.87 (t, J = 7.6 Hz, 2H), 4.75 - 4.63 (m, 2H), 4.54 - 4.34 (m, 1H), 4.11 - 3.95 (m, 3H), 3.86 (d, J = 13.2 Hz, 1H), 3.66 (s, 1H), 3.54 (s, 3H), 3.47 (s, 2H), 3.37 (d, J = 14.4 Hz, 2H), 2.83 (t, J = 8.0 Hz, 2H), 2.71 (d, J = 8.8 Hz, 2H), 2.20 - 2.07 (m, 2H), 1.92 (d, J = 8.9 Hz, 2H), 1.04 (s, 3H), 1.00 (s, 3H), 0.75 (s, 8H).

**EXAMPLE 191**

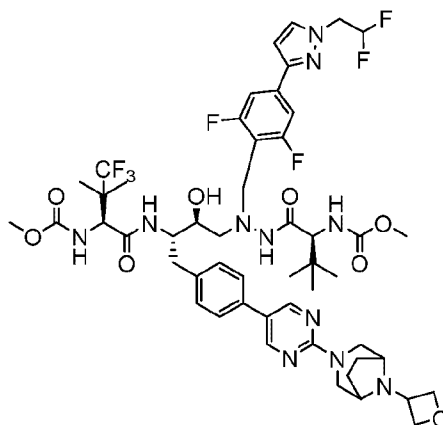
- Methyl ((5S,8S,9S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(2-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidin-5-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate. (191)** Intermediates: **I2**, **P10** and **S6a**. MS (ESI) m/z 1132.8 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.64 (s, 2H), 8.14 (d, J = 9.4 Hz, 1H), 7.87 (d, J = 8.6 Hz, 0H), 7.73 (d, J = 2.4 Hz, 1H), 7.55 (dt, J = 15.4, 7.4 Hz, 1H), 7.50 - 7.21 (m, 6H), 7.09 (d, J = 9.9 Hz, 1H), 6.83 (d, J = 9.8 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.21 (tt, J = 55.3, 3.9 Hz, 1H), 5.18 (s, 1H), 5.02 - 4.89 (m, 2H), 4.73 (d, J = 5.1 Hz, 1H), 4.59 (td, J = 14.1, 13.7, 6.4 Hz, 3H), 4.52 (s, 1H), 4.46 (d, J = 9.7 Hz, 1H), 4.30 (d, J = 9.9 Hz, 1H), 4.13 (d, J = 13.1 Hz, 2H), 3.99 - 3.87 (m, 2H), 3.87 - 3.69 (m,

3H), 3.64 (s, 3H), 3.57 (s, 2H), 2.97 - 2.84 (m, 3H), 2.84 - 2.73 (m, 1H), 2.34 (s, 2H), 1.44 (d, J = 16.1 Hz, 1H), 1.29 (s, 2H), 1.26 (s, 2H), 1.14 (d, J = 4.9 Hz, 6H), 1.10 (s, 3H), 1.02 (s, 3H).



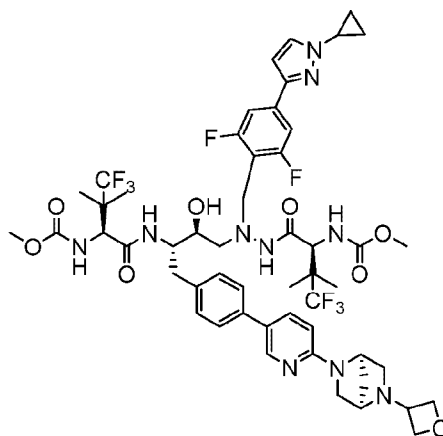
EXAMPLE 192

- 5 **methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(4-(2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-**
4,7,11,12-tetraazahexadecan-14-yl)carbamate (192). Intermediates: **I3**, **P4** and **S7a**. MS (ESI)
 m/z 1078.1 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.65 (s, 3H), 8.14 (d, J = 9.1 Hz,
 10 1H), 8.09 (d, J = 2.8 Hz, 2H), 7.52 (t, J = 59.8 Hz, 2H), 7.43 (dd, J = 12.4, 8.0 Hz, 6H), 7.31 (d,
 J = 7.8 Hz, 3H), 6.92 (d, J = 2.8 Hz, 2H), 6.83 (d, J = 9.8 Hz, 1H), 4.96 (t, J = 7.6 Hz, 3H), 4.46
 (d, J = 9.6 Hz, 2H), 4.13 (d, J = 13.6 Hz, 7H), 3.97 (d, J = 13.1 Hz, 2H), 3.75 (s, 2H), 3.62 (s,
 5H), 3.56 (s, 4H), 3.46 (d, J = 14.3 Hz, 4H), 2.92 (t, J = 8.5 Hz, 2H), 2.81 (d, J = 10.7 Hz, 3H),
 2.21 (d, J = 11.4 Hz, 3H), 2.01 (d, J = 9.0 Hz, 3H), 1.27 (d, J = 13.9 Hz, 1H), 1.13 (s, 6H), 1.10
 15 (s, 5H), 0.84 (s, 14H).

**EXAMPLE 193**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-(4-(2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-

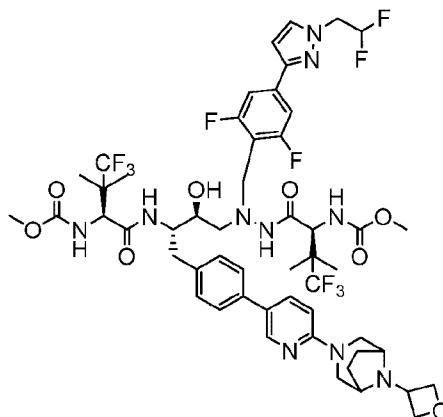
5 **yl)pyrimidin-5-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (193). Intermediates: I3, P10 and S7a. MS (ESI) m/z 1092.3 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.65 (s, 2H), 8.14 (d, J = 9.2 Hz, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.39 (dd, J = 17.0, 8.2 Hz, 4H), 7.31 (d, J = 7.8 Hz, 2H), 6.83 (d, J = 9.8 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.21 (tt, J = 55.4, 3.9 Hz, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.76 (s, 1H), 4.59 (td, J = 14.3, 4.0 Hz, 2H), 4.49 - 4.41 (m, 1H), 4.12 (d, J = 20.4 Hz, 4H), 3.96 (d, J = 13.1 Hz, 1H), 3.76 (s, 2H), 3.62 (s, 3H), 3.56 (s, 3H), 3.47 (d, J = 14.5 Hz, 2H), 2.92 (t, J = 8.4 Hz, 2H), 2.80 (d, J = 9.5 Hz, 2H), 2.26 - 2.10 (m, 2H), 2.01 (d, J = 9.2 Hz, 2H), 1.13 (s, 3H), 1.09 (s, 3H), 0.85 (s, 9H).**



EXAMPLE 194

Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(6-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (194)

Intermediates: **I2**, **P13** and **S6a**. MS (ESI) m/z 1092.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.20 (s, 1H), 8.10 (d, $J = 9.2$ Hz, 1H), 7.87 (d, $J = 9.0$ Hz, 1H), 7.60 (d, $J = 2.4$ Hz, 1H), 7.32 (d, $J = 7.9$ Hz, 2H), 7.23 (dd, $J = 14.4, 8.2$ Hz, 4H), 6.76 (d, $J = 9.4$ Hz, 2H), 6.54 (d, $J = 2.4$ Hz, 1H), 4.93 (s, 1H), 4.61 - 4.53 (m, 1H), 4.52 - 4.46 (m, 1H), 4.45 - 4.27 (m, 2H), 4.21 (d, $J = 9.9$ Hz, 1H), 4.03 (d, $J = 13.0$ Hz, 2H), 3.83 (d, $J = 13.0$ Hz, 1H), 3.72 (d, $J = 9.6$ Hz, 1H), 3.66 - 3.56 (m, 1H), 3.55 (s, 3H), 3.46 (s, 3H), 2.82 (d, $J = 7.2$ Hz, 0H), 2.70 (d, $J = 9.8$ Hz, 1H), 2.22 (s, 2H), 1.05 (d, $J = 5.1$ Hz, 8H), 0.98 (d, $J = 16.3$ Hz, 3H), 0.92 (s, 2H).



15

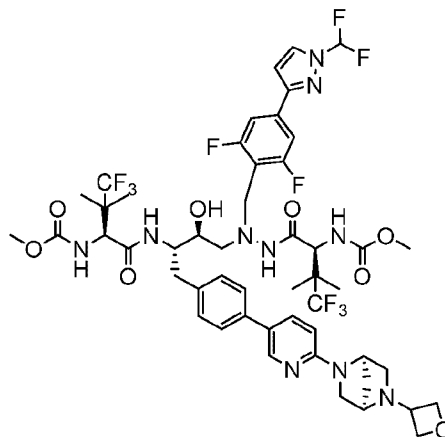
EXAMPLE 195

methyl ((5S,8S,9S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (195).

Intermediates: **I2**, **P10** and **S3c**. MS (ESI) m/z 1146.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.29 (s, 1H), 8.07 (d, $J = 9.3$ Hz, 1H), 7.83 (d, $J = 9.0$ Hz, 1H), 7.64 (d, $J = 2.4$ Hz, 1H), 7.33 (d, $J = 8.1$ Hz, 2H), 7.28 (d, $J = 8.4$ Hz, 1H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.02 (d, $J = 9.8$ Hz, 1H), 6.89 (d, $J = 8.9$ Hz, 1H), 6.74 (d, $J = 9.8$ Hz, 1H), 6.64 (d, $J = 2.5$ Hz, 1H), 6.12 (tt, $J = 55.3, 3.9$ Hz, 1H), 4.86 (t, $J = 7.6$ Hz, 2H), 4.74 - 4.66 (m, 2H), 4.51 (td, $J = 14.3, 3.9$ Hz, 2H),

4.45 - 4.33 (m, 2H), 4.26 - 4.09 (m, 3H), 4.03 (d, J = 8.7 Hz, 4H), 3.84 (d, J = 13.2 Hz, 1H), 3.67 (s, 1H), 3.54 (s, 3H), 3.46 (s, 2H), 3.32 (s, 1H), 3.29 (d, J = 1.7 Hz, 1H), 2.91 - 2.73 (m, 2H), 2.70 (d, J = 9.4 Hz, 1H), 2.14 (t, J = 6.4 Hz, 2H), 2.01 (d, J = 8.5 Hz, 2H), 1.05 (d, J = 3.7 Hz, 6H), 1.01 (s, 3H), 0.92 (s, 2H).

5

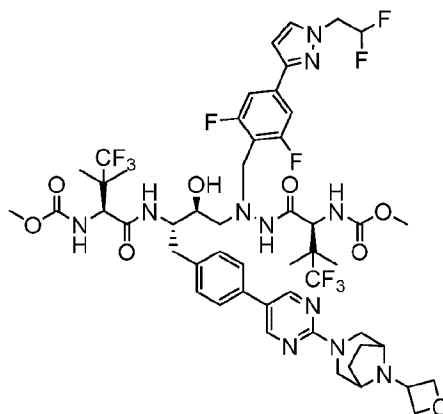


EXAMPLE 196

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(6-((1R,4R)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (196).

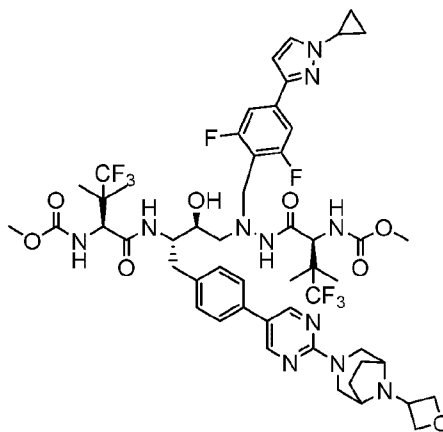
Intermediates: **I2**, **P4** and **S6a**. MS (ESI) m/z 1117.2 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.20 (s, 1H), 8.07 (d, J = 9.2 Hz, 1H), 8.01 (d, J = 2.7 Hz, 1H), 7.88 (d, J = 8.9 Hz, 1H), 7.44 (t, J = 59.8 Hz, 1H), 7.34 (dd, J = 11.9, 8.1 Hz, 3H), 7.21 (d, J = 7.9 Hz, 2H), 7.02 (d, J = 10.0 Hz, 1H), 6.84 (d, J = 2.7 Hz, 1H), 6.75 (t, J = 10.2 Hz, 1H), 5.01 - 4.89 (m, 1H), 4.59 (dd, J = 8.3, 4.8 Hz, 1H), 4.51 (dd, J = 8.0, 5.0 Hz, 1H), 4.37 (dd, J = 19.9, 10.1 Hz, 3H), 4.20 (d, J = 10.0 Hz, 1H), 4.06 (d, J = 13.2 Hz, 2H), 3.85 (d, J = 13.2 Hz, 1H), 3.81 - 3.61 (m, 2H), 3.56 (d, J = 4.6 Hz, 3H), 3.53 - 3.43 (m, 2H), 2.82 (d, J = 9.0 Hz, 2H), 2.75 - 2.61 (m, 1H), 2.22 (s, 2H), 1.05 (s, 6H), 1.01 (s, 3H), 0.92 (s, 3H).

20

**EXAMPLE 197**

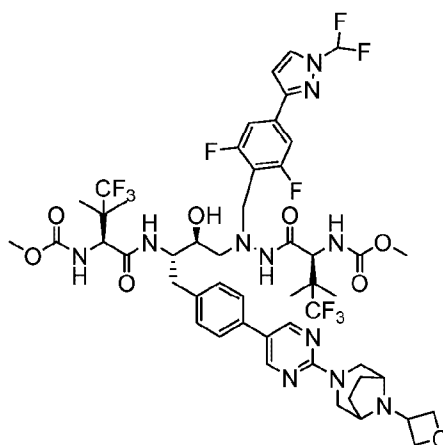
Methyl ((5S,8S,9S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (197).

Intermediates: **I2**, **P10** and **S7a**. MS (ESI) m/z 1146.4 $[M+H]^+$ 1H NMR (400 MHz, Methanol- d_4) δ 8.65 (s, 2H), 8.15 (d, $J = 9.4$ Hz, 1H), 7.73 (d, $J = 2.4$ Hz, 1H), 7.41 (d, $J = 8.0$ Hz, 2H), 7.37 (d, $J = 8.4$ Hz, 2H), 7.31 (d, $J = 7.9$ Hz, 2H), 7.10 (d, $J = 9.9$ Hz, 1H), 6.84 (d, $J = 9.7$ Hz, 1H), 6.73 (d, $J = 2.4$ Hz, 1H), 6.21 (tt, $J = 55.3, 4.0$ Hz, 1H), 4.96 (t, $J = 7.6$ Hz, 2H), 4.84 – 4.73 (m, 4H), 4.60 (td, $J = 14.3, 3.9$ Hz, 2H), 4.49 – 4.42 (m, 1H), 4.33 – 4.26 (m, 1H), 4.21 – 4.08 (m, 4H), 3.94 (d, $J = 13.2$ Hz, 1H), 3.81 – 3.71 (m, 1H), 3.63 (s, 3H), 3.56 (s, 3H), 3.47 (d, $J = 14.4$ Hz, 2H), 2.99 – 2.74 (m, 4H), 2.28 – 2.12 (m, 2H), 2.05 – 1.91 (m, 2H), 1.15 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H). ^{19}F NMR (376 MHz, Methanol- d_4) δ -77.37, -77.69, -77.80, -115.42, -125.27 (dt, $J = 55.2, 14.3$ Hz).



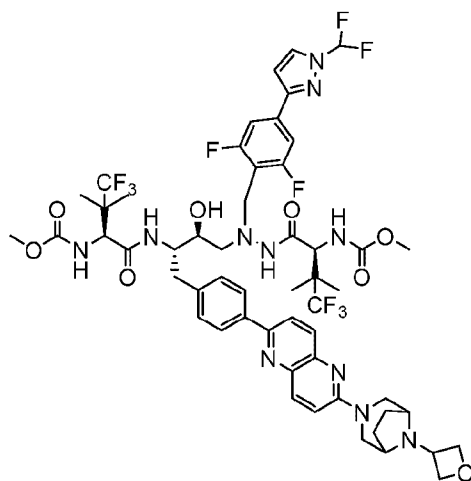
EXAMPLE 198

- methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-**
- 5 **4,7,11,12-tetraazahexadecan-14-yl)carbamate (198).** Intermediates: **I2**, **P13** and **S7a**. MS (ESI) m/z 1122.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.56 (s, 2H), 8.07 (d, J = 9.3 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 7.9 Hz, 2H), 7.28 - 7.16 (m, 4H), 7.03 (d, J = 10.0 Hz, 1H), 6.75 (d, J = 9.8 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 4.87 (t, J = 7.6 Hz, 2H), 4.76 - 4.70 (m, 2H), 4.67 (s, 1H), 4.37 (d, J = 9.9 Hz, 1H), 4.21 (d, J = 10.0 Hz, 1H), 4.12 - 3.99 (m, 4H),
- 10 3.84 (d, J = 13.2 Hz, 1H), 3.66 (s, 1H), 3.60 (tt, J = 7.3, 3.9 Hz, 1H), 3.55 (s, 3H), 3.47 (s, 3H), 3.38 (d, J = 14.3 Hz, 2H), 2.89 - 2.62 (m, 4H), 2.18 - 2.06 (m, 2H), 1.96 - 1.85 (m, 2H), 1.12 - 0.93 (m, 13H), 0.93 (s, 3H).

**EXAMPLE 199**

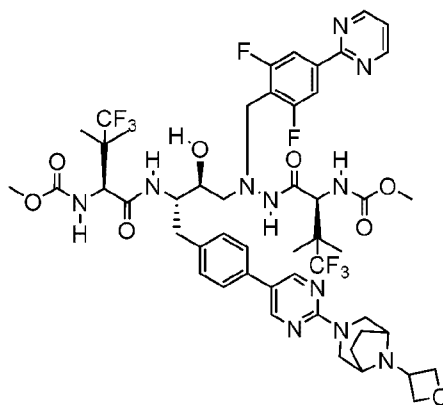
- 15 **Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (199).**
- Intermediates: **I2**, **P4** and **S7a**. MS (ESI) m/z 1132.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.56 (s, 2H), 8.08 (d, J = 9.4 Hz, 1H), 8.01 (d, J = 2.7 Hz, 1H), 7.44 (t, J = 59.9, 59.5 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 9.9 Hz, 1H), 6.84 (d, J = 2.7 Hz, 1H), 6.77 (d, J = 9.9 Hz, 1H), 4.87 (t, J = 7.6 Hz, 2H), 4.72 (dd, J = 8.3, 5.0 Hz, 2H), 4.69 (s, 2H), 4.37 (d, J = 9.8 Hz, 1H), 4.20 (d, J = 10.0 Hz, 1H), 4.12 - 3.96 (m, 4H), 3.85 (d, J = 13.1 Hz, 1H), 3.67 (s, 1H), 3.55 (s, 3H), 3.47 (s, 3H), 3.37 (d, J = 14.3 Hz, 2H),
- 20

2.87 - 2.75 (m, 3H), 2.75 - 2.66 (m, 1H), 1.92 (d, J = 9.2 Hz, 2H), 1.05 (s, 6H), 1.01 (s, 3H), 0.93 (s, 3H).



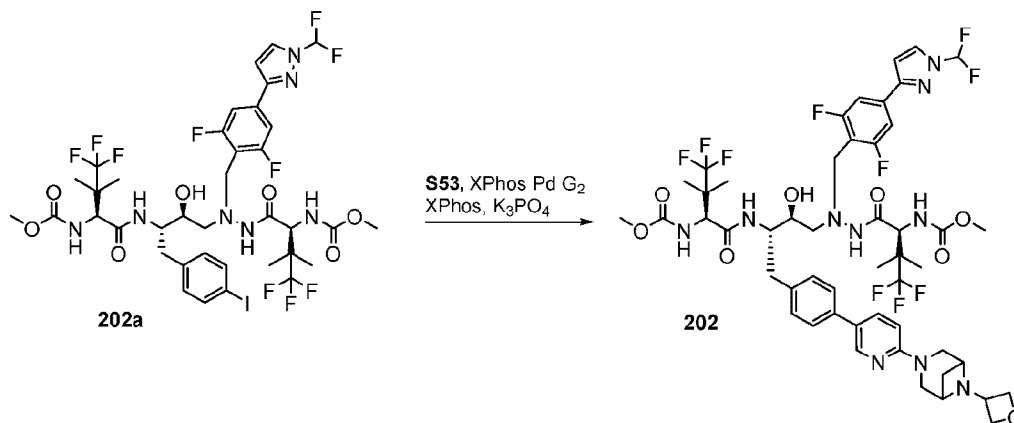
EXAMPLE 200

- 5 **Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-1,5-naphthyridin-2-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (200).**
 Intermediates: **I2**, **P4** and **S31b**. MS (ESI) m/z 1182.3 [M+H]⁺. ¹H NMR (400 MHz, Methanol-
 10 d4) δ 8.22 - 8.04 (m, 3H), 8.01 (d, J = 2.7 Hz, 2H), 7.85 (d, J = 7.9 Hz, 2H), 7.44 (t, J = 59.7 Hz, 1H), 7.41 (d, J = 9.5 Hz, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 4.89 (t, J = 7.6 Hz, 2H), 4.74 (dd, J = 8.2, 5.1 Hz, 2H), 4.53 (d, J = 14.1 Hz, 2H), 4.37 (s, 1H), 4.21 (s, 1H), 4.16 - 4.01 (m, 4H), 3.86 (d, J = 13.1 Hz, 1H), 3.71 (s, 1H), 3.54 (s, 3H), 3.44 (d, J = 13.8 Hz, 2H), 3.41 - 3.33 (m, 3H), 2.95 - 2.63 (m, 5H), 2.22 - 2.10 (m, 2H), 2.11 -
 15 1.96 (m, 2H), 1.25 - 1.16 (m, 1H), 1.05 (s, 6H), 1.02 (s, 3H), 0.93 (s, 3H).

**EXAMPLE 201**

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyrimidin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (201). Intermediates: **I2**, **P16** and **S7a**. MS (ESI) m/z 1094.8 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.86 (d, $J = 4.9$ Hz, 1H), 8.65 (s, 1H), 8.14 (d, $J = 9.4$ Hz, 0H), 7.96 (d, $J = 8.6$ Hz, 1H), 7.48 - 7.37 (m, 2H), 7.32 (d, $J = 7.9$ Hz, 1H), 7.08 (d, $J = 10.0$ Hz, 0H), 6.83 (d, $J = 9.9$ Hz, 0H), 4.96 (t, $J = 7.6$ Hz, 1H), 4.83 (s, 8H), 4.53 - 4.41 (m, 0H), 4.37 - 4.25 (m, 1H), 4.23 - 4.07 (m, 2H), 3.98 (d, $J = 13.1$ Hz, 1H), 3.78 (s, 0H), 3.65 (s, 2H), 3.56 (s, 1H), 3.52 - 3.39 (m, 1H), 3.00 - 2.75 (m, 2H), 2.26 - 2.14 (m, 1H), 2.02 (t, $J = 7.0$ Hz, 1H), 1.12 (d, $J = 13.2$ Hz, 5H), 1.02 (s, 1H).

15

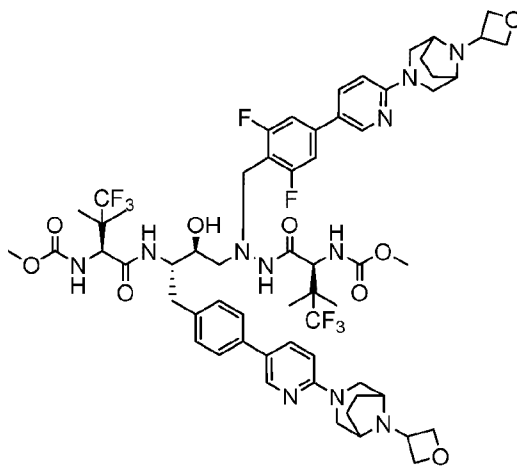
EXAMPLE 202

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-8-(4-iodobenzyl)-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (202a).

- 5 The title compound **202a** was prepared according to the method presented for the synthesis of compound **1a** but instead utilizing **P4**. MS (ESI) m/z 1014.4 $[M+H]^+$.

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(6-(6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (202)

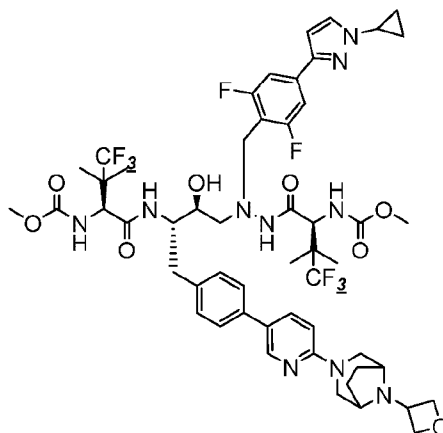
- 10 In a 20 mL vial, a solution of **202a** (50 mg, 0.05 mmol), **S53** (38.1 mg, 0.08 mmol), XPhos Pd G2 (16.4 mg, 0.01 mmol), 2-(Dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (5.6 mg, 0.01 mmol) and Potassium phosphate tribasic (106 mg, 0.5 mmol) in dioxane (3 mL) and water (1 mL) was degassed for 10 min with argon. The mixture was heated to 100 °C for 1 h. The reaction
- 15 was cooled to room temperature, diluted with MeOH, filtered through Celite, and the filtrate was concentrated under vacuum. The residue was purified by HPLC and the product was lyophilized to afford **202**. MS (ESI) m/z 1117.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.31 (s, 1H), 8.11 (d, J = 9.3 Hz, 1H), 8.02 (d, J = 2.7 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.44 (t, J = 59.8 Hz, 1H), 7.35 (dd, J = 8.1, 3.9 Hz, 4H), 7.22 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 10.0 Hz, 1H), 6.90 -
- 20 6.80 (m, 2H), 6.78 (d, J = 9.8 Hz, 0H), 4.88 (t, J = 7.3 Hz, 2H), 4.52 (dd, J = 8.1, 4.3 Hz, 4H), 4.38 (d, J = 9.5 Hz, 1H), 4.21 (d, J = 9.9 Hz, 1H), 4.06 (d, J = 12.5 Hz, 4H), 3.87 (t, J = 14.4 Hz, 3H), 3.68 (s, 1H), 3.55 (s, 3H), 3.46 (s, 2H), 2.94 - 2.76 (m, 3H), 2.76 - 2.64 (m, 1H), 2.03 (d, J = 11.1 Hz, 1H), 1.05 (s, 6H), 1.01 (s, 3H), 0.91 (s, 3H).



EXAMPLE 203

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (203).

Intermediates: **I2**, **P22** and **S60**. MS (ESI) m/z 1259.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.47 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 7.94 (s, 2H), 7.42 (d, $J = 7.9$ Hz, 2H), 7.30 (d, $J = 7.9$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 2H), 6.99 (dd, $J = 19.7, 9.0$ Hz, 2H), 4.95 (dd, $J = 7.5, 2.8$ Hz, 4H), 4.85 - 4.72 (m, 5H), 4.61 - 4.24 (m, 7H), 4.16 (s, 6H), 3.73 - 3.44 (m, 6H), 3.44 - 3.34 (m, 3H), 2.99 - 2.73 (m, 2H), 2.35 - 2.21 (m, 3H), 1.29 (s, 18H), 1.19 - 0.96 (m, 10H).

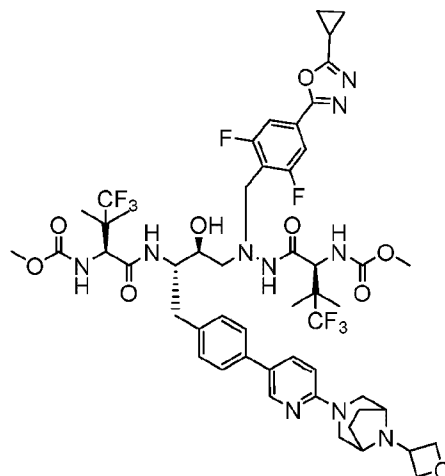


15

EXAMPLE 204

Methyl ((5S,8S,9S,14S)-11-(4-(1-cyclopropyl-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (204).

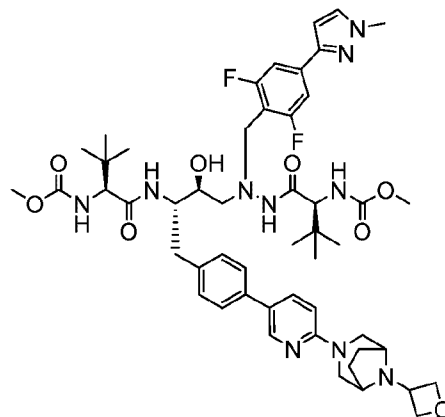
Intermediates: **I2**, **P13** and **S60**. MS (ESI) m/z 1121.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.37 (s, 1H), 8.19 (s, 0H), 7.69 (d, $J = 2.5$ Hz, 1H), 7.53 - 7.22 (m, 7H), 6.98 (d, $J = 8.8$ Hz, 1H), 6.63 (d, $J = 2.5$ Hz, 1H), 4.54 (d, $J = 59.0$ Hz, 0H), 4.38 - 4.24 (m, 4H), 4.24 - 3.93 (m, 6H), 3.64 (d, $J = 6.0$ Hz, 5H), 3.56 - 3.39 (m, 6H), 2.09 (d, $J = 8.5$ Hz, 2H), 1.42 - 0.62 (m, 16H).

**EXAMPLE 205**

Methyl ((5S,8S,9S,14S)-11-(4-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-2,6-difluorobenzyl)-

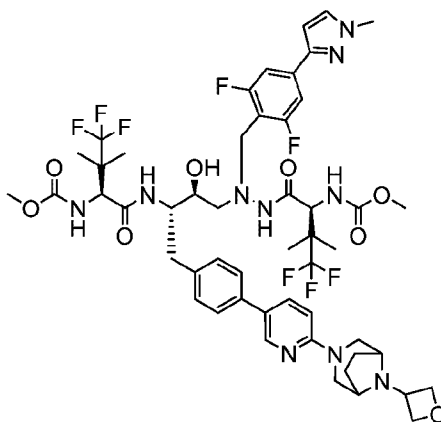
- 5 **16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(6-(8-(oxetan-3-yl)-3,8-**
diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-
methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (205).

Intermediates: **I3**, **P40** and **S60**. MS (ESI) m/z 1123.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol-
 d_4) δ 8.39 – 8.33 (m, 1H), 8.10 (dd, $J = 19.9, 9.2$ Hz, 2H), 7.53 (d, $J = 7.3$ Hz, 3H), 7.45 (d, $J =$
 10 7.9 Hz, 3H), 7.32 (d, $J = 7.9$ Hz, 3H), 7.13 (dd, $J = 21.7, 9.5$ Hz, 2H), 4.99 – 4.83 (m, 4H), 4.61
 – 4.50 (m, 2H), 4.50 – 4.43 (m, 1H), 4.35 – 4.24 (m, 5H), 4.18 (d, $J = 11.8$ Hz, 5H), 3.78 (s,
 1H), 3.67 (s, 4H), 3.59 (d, $J = 13.0$ Hz, 7H), 3.01 – 2.76 (m, 5H), 2.35 – 2.23 (m, 4H), 2.14 (t, J
 = 6.9 Hz, 3H), 1.32 – 1.10 (m, 19H), 1.10 – 0.95 (m, 5H).

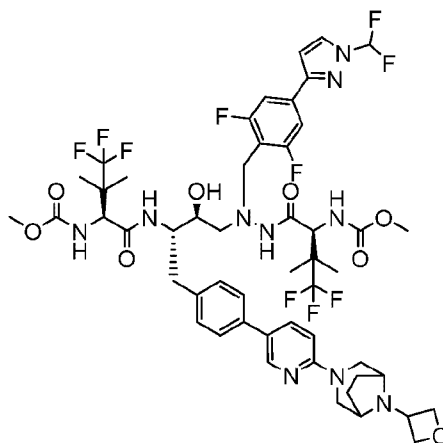


EXAMPLE 206

- Methyl ((5S,8S,9S,14S)-5-(tert-butyl)-11-(2,6-difluoro-4-(1-methyl-1H-pyrazol-3-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-(4-(6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)benzyl)-3,6,13-trioxo-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (206).** Intermediates: **I1**, **P41** and **S60**. MS (ESI) m/z 987.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.36 (d, $J = 2.4$ Hz, 1H), 7.61 (d, $J = 2.3$ Hz, 1H), 7.44 (d, $J = 7.9$ Hz, 2H), 7.36 – 7.28 (m, 4H), 7.07 (d, $J = 9.0$ Hz, 1H), 6.64 (d, $J = 2.3$ Hz, 1H), 4.95 (t, $J = 7.5$ Hz, 2H), 4.83 (dd, $J = 8.0, 5.1$ Hz, 2H), 4.53 (dq, $J = 12.1, 6.2, 5.7$ Hz, 1H), 4.28 (dd, $J = 14.1, 2.4$ Hz, 2H), 4.19 – 4.06 (m, 4H), 4.00 – 3.89 (m, 5H), 3.75 (s, 2H), 3.60 (d, $J = 16.6$ Hz, 6H), 3.49 (d, $J = 13.6$ Hz, 2H), 2.95 (td, $J = 12.3, 11.7, 7.2$ Hz, 2H), 2.87 – 2.79 (m, 2H), 2.29 – 2.21 (m, 2H), 2.20 – 2.08 (m, 2H), 0.88 (s, 9H), 0.82 (s, 9H).

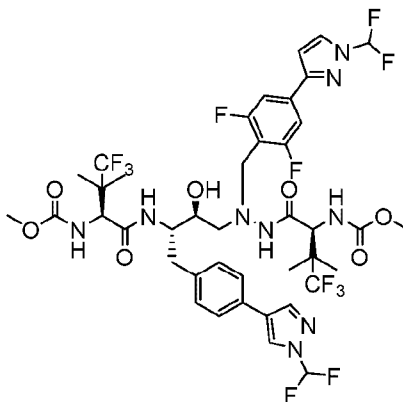
**EXAMPLE 207**

- Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(1-methyl-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (207).** Intermediates: **I2**, **P41** and **S60**. MS (ESI) m/z 1095.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.36 (d, $J = 2.3$ Hz, 1H), 8.15 (d, $J = 9.3$ Hz, 1H), 7.62 (d, $J = 2.3$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 2H), 7.33 (dd, $J = 8.2, 5.3$ Hz, 4H), 7.12 (dd, $J = 19.4, 9.5$ Hz, 1H), 6.65 (d, $J = 2.3$ Hz, 1H), 4.95 (t, $J = 7.5$ Hz, 2H), 4.85 (dd, $J = 8.1, 5.1$ Hz, 2H), 4.58 – 4.44 (m, 2H), 4.35 – 4.23 (m, 3H), 4.22 – 4.09 (m, 4H), 3.93 (s, 4H), 3.65 (s, 3H), 3.60 – 3.52 (m, 4H), 3.01 – 2.89 (m, 2H), 2.88 – 2.74 (m, 2H), 2.30 – 2.23 (m, 2H), 2.14 (t, $J = 6.9$ Hz, 2H), 1.18 – 1.08 (m, 8H), 1.02 (s, 3H).

**EXAMPLE 208**

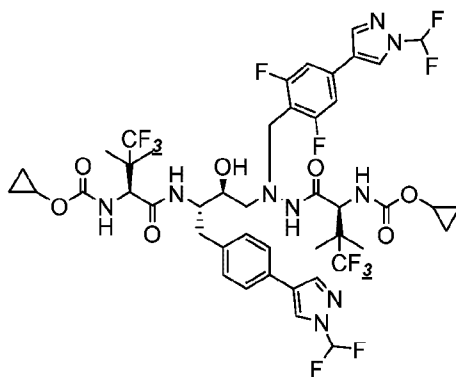
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-(6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (208).

Intermediates: **I2**, **P4** and **S60**. MS (ESI) m/z 1131.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.36 (d, $J = 2.3$ Hz, 1H), 8.16 – 8.02 (m, 2H), 7.44 (h, $J = 4.1, 3.5$ Hz, 3H), 7.40 – 7.29 (m, 2H), 7.14 (d, $J = 9.1$ Hz, 1H), 6.93 (d, $J = 2.7$ Hz, 1H), 4.95 (t, $J = 7.5$ Hz, 2H), 4.58 – 4.43 (m, 2H), 4.34 – 4.23 (m, 3H), 4.21 – 4.11 (m, 3H), 4.00 – 3.91 (m, 1H), 3.77 (s, 1H), 3.67 – 3.52 (m, 6H), 3.01 – 2.86 (m, 3H), 2.80 (dd, $J = 12.6, 9.1$ Hz, 1H), 2.31 – 2.23 (m, 2H), 2.22 – 2.08 (m, 2H), 1.13 (d, $J = 14.1$ Hz, 7H), 1.03 (s, 2H).

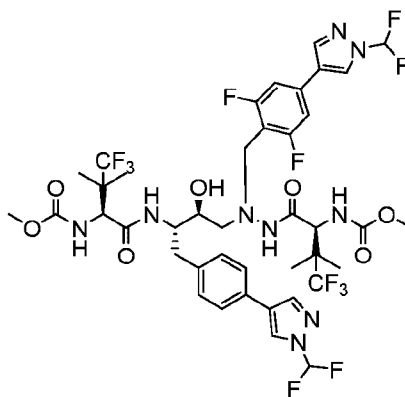


EXAMPLE 209

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-8-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (209). Intermediates: **I2**, **P4** and 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole. MS (ESI) m/z 1004.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.32 (s, 2H), 8.09 (d, $J = 2.7$ Hz, 2H), 8.02 (s, 2H), 7.66 (d, $J = 19.3$ Hz, 1H), 7.56 – 7.31 (m, 13H), 7.24 (d, $J = 8.0$ Hz, 5H), 6.91 (d, $J = 2.7$ Hz, 2H), 4.46 (s, 2H), 4.31 (s, 2H), 4.20 – 4.07 (m, 5H), 3.93 (d, $J = 13.1$ Hz, 2H), 3.76 (s, 2H), 3.64 (s, 6H), 3.56 (s, 6H), 3.35 (s, 1H), 2.95 – 2.84 (m, 7H), 2.79 (dd, $J = 12.6, 9.2$ Hz, 3H), 1.24 – 1.09 (m, 28H), 1.02 (s, 6H).

**EXAMPLE 210**

Cyclopropyl ((S)-1-(2-((2S,3S)-3-((S)-2-((cyclopropoxycarbonyl)amino)-4,4,4-trifluoro-3,3-dimethylbutanamido)-4-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)phenyl)-2-hydroxybutyl)-2-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)hydrazinyl)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)carbamate (210). Intermediates: **I2a**, **A4**, **P7** and 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole MS (ESI) m/z 1056.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.53 (d, $J = 0.8$ Hz, 1H), 8.33 (s, 1H), 8.12 (s, 1H), 8.03 (s, 1H), 7.52 – 7.45 (m, 4H), 7.25 (d, $J = 8.2$ Hz, 4H), 4.47 (s, 1H), 4.32 (s, 1H), 4.14 (s, 1H), 4.01 (td, $J = 5.6, 3.0$ Hz, 1H), 3.93 (d, $J = 12.1$ Hz, 2H), 3.76 (d, $J = 8.5$ Hz, 1H), 2.94 – 2.73 (m, 5H), 2.01 (s, 2H), 1.23 (t, $J = 7.1$ Hz, 2H), 1.17 – 1.09 (m, 10H), 1.02 (s, 3H), 0.69 – 0.51 (m, 8H).

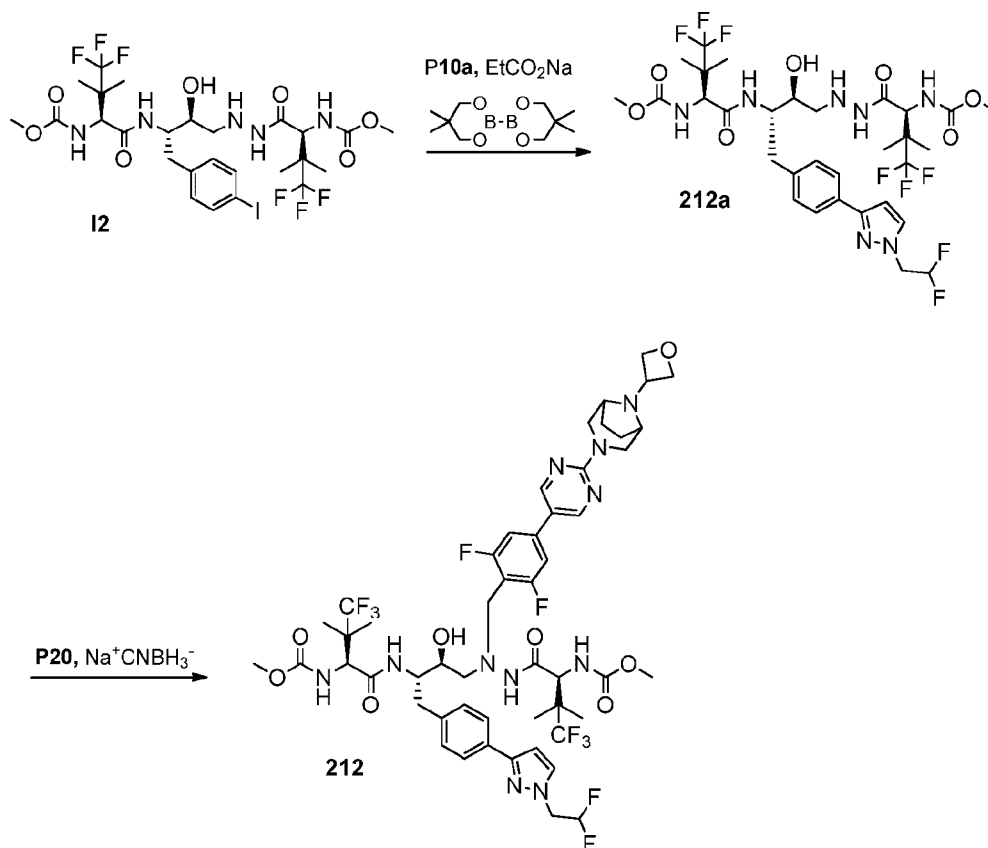


EXAMPLE 211

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-8-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (211). Intermediates: **I2**, **P7** and 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole MS (ESI) m/z 1004.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.44 (d, $J = 0.7$ Hz, 1H), 8.24 (s, 1H), 8.03 (s, 1H), 7.93 (s, 1H), 7.41 (s, 1H), 7.39 – 7.35 (m, 3H), 7.25 (d, $J = 10.6$ Hz, 1H), 7.15 (d, $J = 8.1$ Hz, 4H), 4.35 (s, 1H), 4.20 (s, 1H), 4.05 – 3.98 (m, 3H), 3.85 (s, 1H), 3.54 (s, 4H), 3.46 (s, 3H), 2.82 – 2.65 (m, 4H), 1.91 (s, 1H), 1.08 – 0.99 (m, 9H), 0.92 (s, 3H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -76.33 – -79.41 (m), -96.67 (dd, $J = 145.1, 59.7$ Hz).

15

20

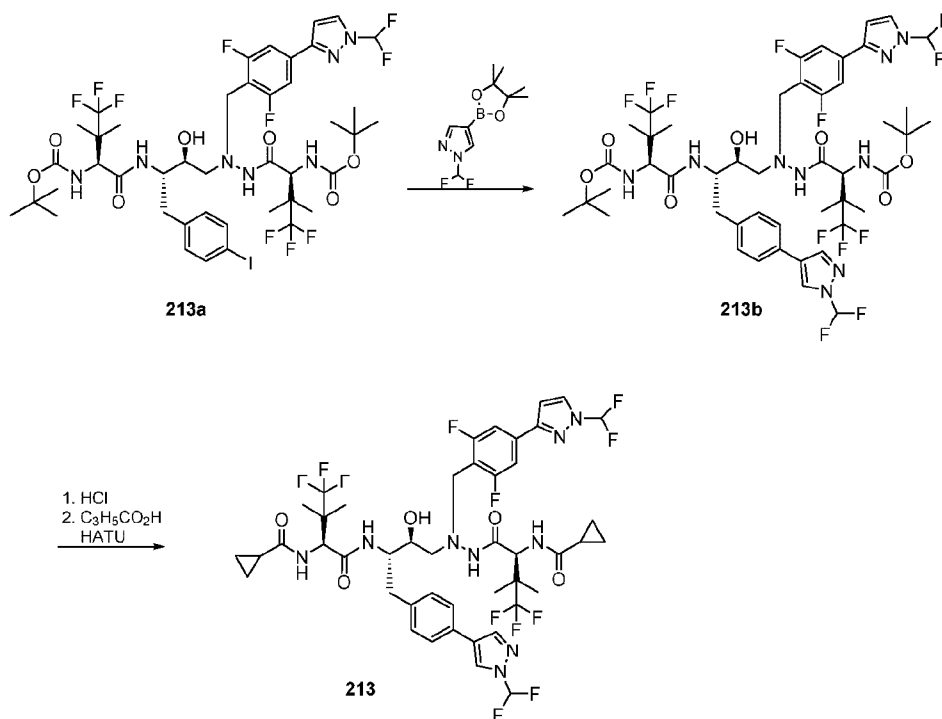
EXAMPLE 212

Synthesis of methyl ((5S,10S,11S,14S)-11-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-10-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,8,12-tetraazahexadecan-14-yl)carbamate (**212a**). The title compound **212a** was prepared according to the method presented for the synthesis of compound **188** but instead utilizing **12** and **P10a**. MS (ESI) m/z 776.3 $[\text{M}+\text{H}]^+$.

Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)benzyl)-8-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (**212**) The title compound **212** was prepared according to the method presented for the synthesis of compound **1a** but instead utilizing **212a** and **P20**. MS (ESI) m/z 1146.3 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, Methanol- d_4) δ 8.71 (s, 2H), 8.11 (d, $J = 9.7$ Hz, 1H), 7.68 (d, $J = 2.4$ Hz, 1H), 7.64 (d, $J = 7.9$ Hz, 2H), 7.25 (s, 1H), 7.21 (d, $J = 8.3$ Hz, 1H), 7.13 (d, $J = 10.1$ Hz, 1H), 6.78 (d, $J = 10.1$ Hz, 1H), 6.63 (d, $J =$

2.4 Hz, 1H), 6.19 (tt, J = 55.6, 3.9 Hz, 1H), 4.96 (t, J = 7.5 Hz, 2H), 4.56 (td, J = 14.3, 3.9 Hz, 2H), 4.43 (d, J = 9.7 Hz, 1H), 4.29 (d, J = 10.0 Hz, 1H), 4.23 - 4.08 (m, 4H), 3.95 (d, J = 13.5 Hz, 1H), 3.73 (s, 1H), 3.63 (s, 3H), 3.55 (s, 3H), 3.52 - 3.43 (m, 2H), 2.93 - 2.73 (m, 3H), 2.25 - 2.17 (m, 2H), 2.06 - 1.94 (m, 2H), 1.15 - 1.12 (m, 6H), 1.11 (s, 3H), 1.01 (s, 3H).

5

EXAMPLE 213

10

Synthesis of tert-butyl ((6S,9S,10S,15S)-12-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-17,17,17-trifluoro-10-hydroxy-9-(4-iodobenzyl)-2,2,16,16-tetramethyl-4,7,14-trioxo-6-(1,1,1-trifluoro-2-methylpropan-2-yl)-3-oxa-5,8,12,13-tetraazaheptadecan-15-yl)carbamate (213a). The title compound 213a was prepared according to the method presented

15 for the synthesis of compound 188 but instead utilizing I2a, A1, and P4.

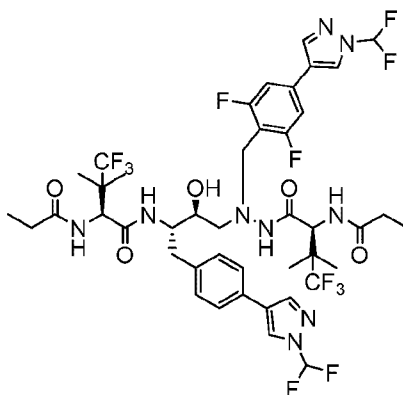
Synthesis of tert-butyl ((6S,9S,10S,15S)-12-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)benzyl)-17,17,17-trifluoro-10-hydroxy-2,2,16,16-tetramethyl-4,7,14-trioxo-6-(1,1,1-trifluoro-2-methylpropan-2-yl)-3-oxa-5,8,12,13-tetraazaheptadecan-15-yl)carbamate (213b). The title compound 213b was

Synthesis of N-((S)-1-(2-((2S,3S)-3-((S)-2-(cyclopropanecarboxamido)-4,4,4-trifluoro-3,3-dimethylbutanamido)-4-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)phenyl)-2-hydroxybutyl)-2-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)hydrazinyl)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)cyclopropanecarboxamide (213). To a solution of 213a (255

N-((S)-1-(2-((2S,3S)-3-((S)-2-(cyclopropanecarboxamido)-4,4,4-trifluoro-3,3-dimethylbutanamido)-4-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)phenyl)-2-hydroxybutyl)-2-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)hydrazinyl)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)cyclopropanecarboxamide (214). The title compound **214** was

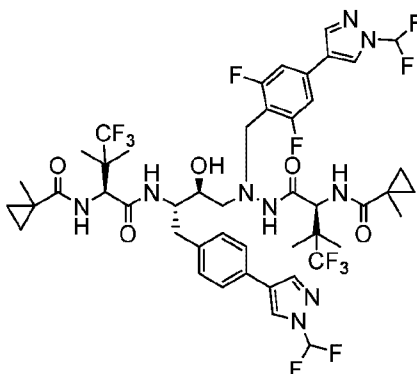
-315-

- 8.33 (d, $J = 0.7$ Hz, 1H), 8.27 (d, $J = 9.8$ Hz, 1H), 8.13 – 8.09 (m, 2H), 8.03 – 7.96 (m, 2H), 7.64 (d, $J = 10.5$ Hz, 1H), 7.52 – 7.45 (m, 3H), 7.34 (d, $J = 10.7$ Hz, 1H), 7.24 (t, $J = 8.5$ Hz, 4H), 4.81 – 4.78 (m, 1H), 4.69 – 4.64 (m, 1H), 4.12 (d, $J = 12.4$ Hz, 2H), 3.91 (d, $J = 13.2$ Hz, 1H), 3.74 (d, $J = 8.9$ Hz, 1H), 2.88 (d, $J = 7.6$ Hz, 3H), 2.77 (dd, $J = 12.5, 9.3$ Hz, 1H), 1.69 (dt, $J = 8.0, 3.7$ Hz, 1H), 1.57 (tt, $J = 8.3, 4.6$ Hz, 1H), 1.29 (d, $J = 0.6$ Hz, 1H), 1.24 (d, $J = 7.7$ Hz, 1H), 1.21 – 1.12 (m, 9H), 1.06 (s, 2H), 0.94 – 0.68 (m, 7H), 0.59 (d, $J = 8.0$ Hz, 1H).

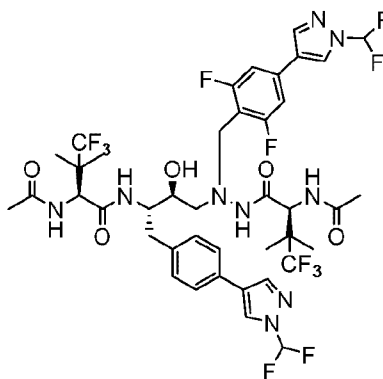


EXAMPLE 215

- (S)-N-((2S,3S)-4-(1-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-2-((S)-4,4,4-trifluoro-3,3-dimethyl-2-propionamidobutanoyl)hydrazinyl)-1-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)phenyl)-3-hydroxybutan-2-yl)-4,4,4-trifluoro-3,3-dimethyl-2-propionamidobutanamide (**215**). The title compound **215** was prepared according to the method presented for the synthesis of compound **213** but instead utilizing **P7** and propionic acid. MS (ESI) m/z 1000.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.54 (d, $J = 0.7$ Hz, 1H), 8.35 (d, $J = 0.7$ Hz, 1H), 8.14 – 8.00 (m, 5H), 7.71 (d, $J = 9.8$ Hz, 1H), 7.64 (d, $J = 10.9$ Hz, 1H), 7.52 – 7.44 (m, 4H), 7.25 (t, $J = 8.6$ Hz, 5H), 4.78 – 4.74 (m, 1H), 4.67 – 4.63 (m, 1H), 4.14 (d, $J = 13.2$ Hz, 2H), 3.92 (d, $J = 13.2$ Hz, 1H), 3.73 (d, $J = 8.7$ Hz, 1H), 2.88 (d, $J = 8.7$ Hz, 4H), 2.76 (dd, $J = 12.7, 9.3$ Hz, 1H), 2.25 – 1.99 (m, 6H), 1.25 – 0.95 (m, 24H).



N-((S)-1-(2-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-2-((2S,3S)-4-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)phenyl)-2-hydroxy-3-((S)-4,4,4-trifluoro-3,3-dimethyl-2-(1-methylcyclopropane-1-carboxamido)butanamido)butyl)hydrazinyl)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)-1-methylcyclopropane-1-carboxamide (216). The title compound **216** was prepared according to the method presented for the synthesis of compound **213** but instead utilizing **P7** and 1-Methylcyclopropanecarboxylic acid. MS (ESI) m/z 1052.7 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.17 (s, 1H), 7.97 (s, 1H), 7.87 (d, $J = 9.5$ Hz, 1H), 7.75 (s, 1H), 7.65 (s, 1H), 7.15 – 7.07 (m, 4H), 6.87 (t, $J = 8.2$ Hz, 4H), 6.42 (d, $J = 9.6$ Hz, 1H), 6.17 (d, $J = 9.6$ Hz, 1H), 4.38 (d, $J = 9.5$ Hz, 1H), 4.27 (d, $J = 9.5$ Hz, 1H), 3.89 – 3.73 (m, 2H), 3.58 – 3.48 (m, 1H), 3.39 (s, 1H), 2.50 (t, $J = 7.6$ Hz, 3H), 2.41 (dd, $J = 12.6, 9.0$ Hz, 1H), 0.95 – 0.54 (m, 25H), 0.22 (d, $J = 3.8$ Hz, 2H), 0.13 (ddd, $J = 9.8, 6.4, 3.6$ Hz, 1H).

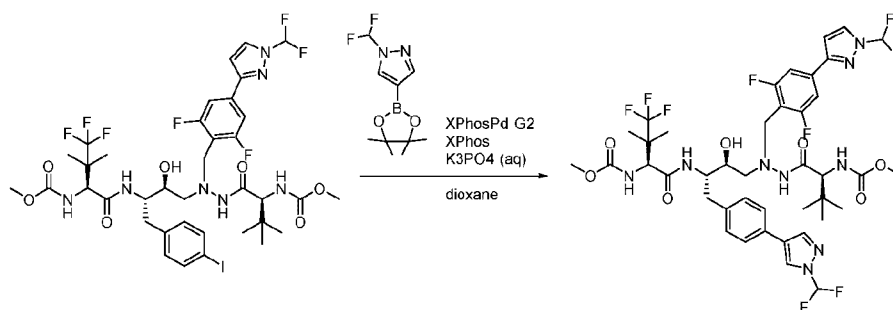


15

-317-

(difluoromethyl)-1H-pyrazol-4-yl)phenyl)-3-hydroxybutan-2-yl)-4,4,4-trifluoro-3,3-

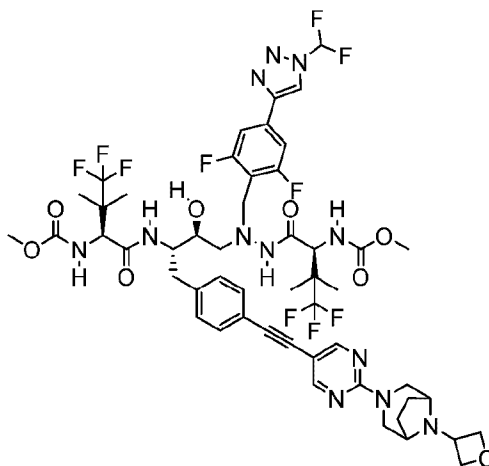
dimethylbutanamide (217). The title compound **217** was prepared according to the method presented for the synthesis of compound **213** but instead utilizing **P7** and Acetic anhydride. MS (ESI) m/z 972.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.55 (s, 1H), 8.36 (s, 1H), 8.16 (d, $J = 21.4$ Hz, 2H), 8.07 (d, $J = 20.2$ Hz, 2H), 7.52 – 7.46 (m, 3H), 7.25 (t, $J = 8.3$ Hz, 4H), 5.48 (d, $J = 0.6$ Hz, 2H), 4.78 – 4.73 (m, 1H), 4.66 – 4.61 (m, 1H), 4.16 (s, 1H), 3.95 – 3.88 (m, 1H), 3.74 (d, $J = 8.5$ Hz, 1H), 2.91 – 2.84 (m, 3H), 2.77 (dd, $J = 12.7, 9.2$ Hz, 1H), 2.15 (s, 1H), 2.03 (d, $J = 0.5$ Hz, 15H), 1.93 (s, 2H), 1.81 (s, 2H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -76.14 – -79.22 (m), -96.72 (dd, $J = 133.4, 59.8$ Hz).

**EXAMPLE 218**

Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-8-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)benzyl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (218). To a solution of methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-9-hydroxy-8-(4-iodobenzyl)-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (0.02g, 0.02mmol) in 1,4-dioxane (0.3mL) was added 1-(Difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.01 g, 0.04 mmol), XPhos Pd G2 (0.005 g, 0.003 mmol), XPhos (0.001g, 0.003 mmol) and Potassium phosphate tribasic (0.01 ml) as an aqueous solution in water (0.01mL). The resulting suspension was sparged with argon for 5 minutes and subsequently placed in a 100 °C aluminum heating block and let stir, heating, overnight under an atmosphere of argon. Upon completion, the residue was purified by reverse phase high pressure liquid chromatography (20-83% acetonitrile in water, 0.1% TFA buffer). The collected product fractions were quenched with sodium bicarbonate (aqueous, saturated), extracted with ethyl acetate and further purified by normal phase silica gel chromatography (0-8% methanol in

dichloromethane) to give methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-8-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)benzyl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate. ES/MS m/z 950.542 $[M+H]^+$.

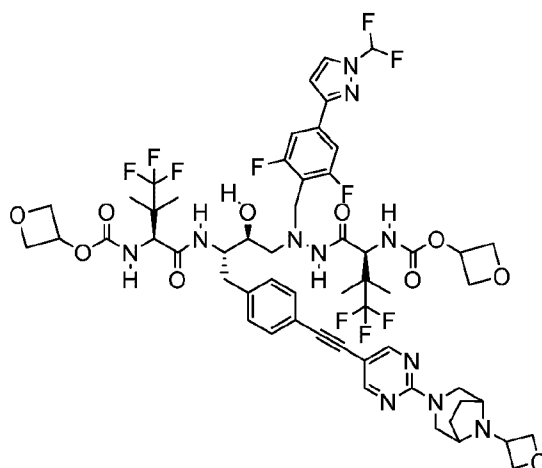
5



EXAMPLE 219

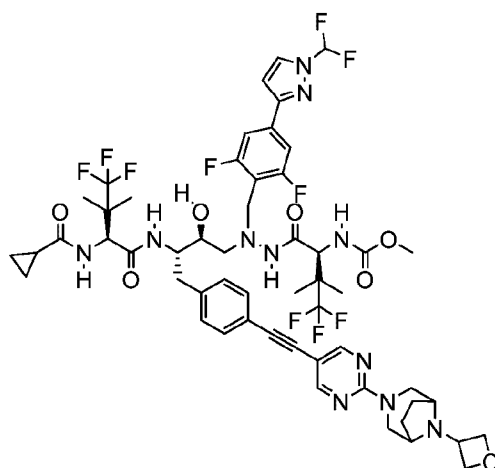
Methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-1,2,3-triazol-4-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (219).

Intermediates: **P44**, **A3**, and **S7**. MS (ESI) m/z 1157.9 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.97 (s, 1H), 8.53 (s, 2H), 8.17 (d, J = 9.8 Hz, 1H), 8.00 (t, J = 58.6 Hz, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 9.9 Hz, 1H), 6.81 (d, J = 9.9 Hz, 1H), 4.96 (dd, J = 8.2, 7.1 Hz, 2H), 4.83 - 4.78 (m, 3H), 4.50 - 4.41 (m, 1H), 4.30 (d, J = 10.0 Hz, 1H), 4.21 - 4.08 (m, 4H), 3.96 (d, J = 13.2 Hz, 1H), 3.74 (d, J = 8.8 Hz, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 3.47 (d, J = 14.5 Hz, 2H), 2.98 - 2.84 (m, 3H), 2.82 - 2.74 (m, 1H), 2.29 - 2.17 (m, 2H), 2.02 - 1.94 (m, 2H), 1.16 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.37, -77.70, -77.82, -98.78 (d, J = 58.6 Hz), -114.26.

**EXAMPLE 220**

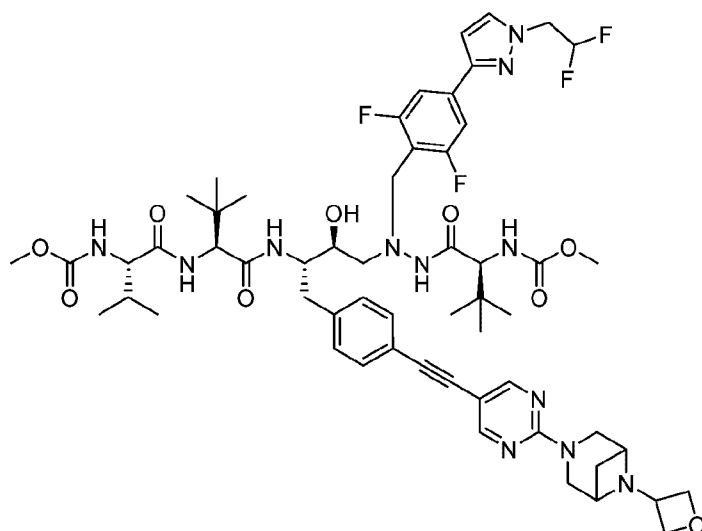
Oxetan-3-yl ((2S)-1-(2-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-2-((2S,3S)-2-hydroxy-4-(4-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)phenyl)-3-((S)-4,4,4-trifluoro-3,3-dimethyl-2-(((oxetan-3-yl)oxy)carbonyl)amino)butanamido)butyl)hydrazinyl)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)carbamate (220). Intermediates: **P4**, **A4**, and **S7**. MS (ESI) m/z 1240.3 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.45 (s, 2H), 8.12 (d, J = 9.3 Hz, 1H), 8.02 (d, J = 2.7 Hz, 1H), 7.45 (t, J = 59.8 Hz, 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 3H), 7.07 (d, J = 10.0 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 5.37 - 5.21 (m, 2H), 4.92 - 4.83 (m, 2H), 4.73 - 4.69 (m, 2H), 4.56 (ddd, J = 12.4, 7.3, 5.2 Hz, 2H), 4.50 - 4.44 (m, 2H), 4.33 (d, J = 10.0 Hz, 1H), 4.20 (d, J = 9.9 Hz, 1H), 4.13 - 3.98 (m, 4H), 3.85 (d, J = 13.1 Hz, 1H), 3.67 (s, 1H), 3.39 - 3.32 (m, 3H), 2.86 - 2.78 (m, 3H), 2.68 (dd, J = 12.6, 8.9 Hz, 1H), 2.14 - 2.08 (m, 2H), 1.92 - 1.83 (m, 2H), 1.09 (s, 3H), 1.07 (s, 3H), 1.05 - 0.99 (m, 3H), 0.99 - 0.93 (m, 3H).

¹⁹F NMR (377 MHz, Methanol-d₄) δ -77.46, -77.56, -77.78, -96.92 (d, J = 59.7 Hz), -114.94.

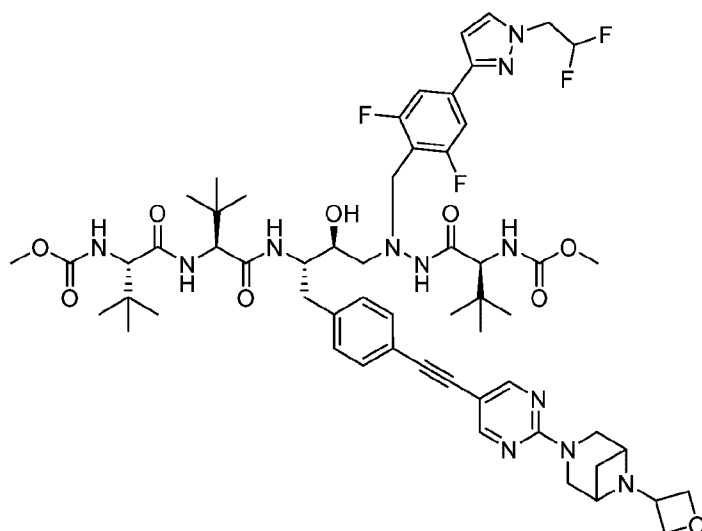
**EXAMPLE 221**

Methyl ((2S)-1-(2-((2S,3S)-3-((S)-2-(cyclopropanecarboxamido)-4,4,4-trifluoro-3,3-dimethylbutanamido)-2-hydroxy-4-(4-((2-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)ethynyl)phenyl)butyl)-2-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)hydrazinyl)-4,4,4-trifluoro-3,3-dimethyl-1-oxobutan-2-yl)carbamate (221).

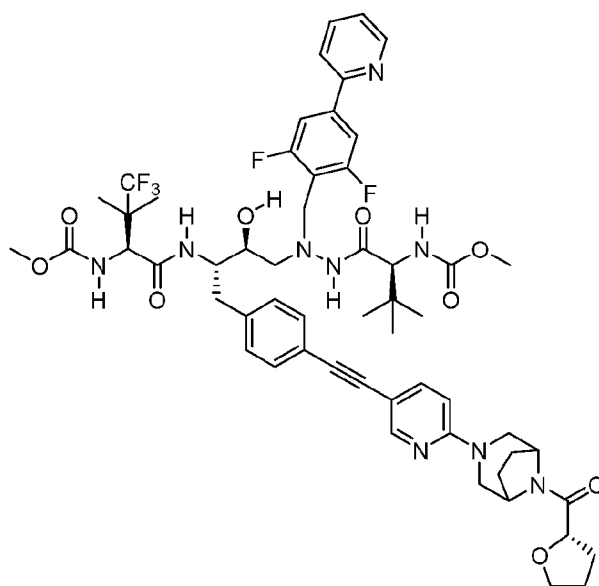
Intermediate I9 was acylated with cyclopropyl carbonyl chloride in the presence of aqueous 2M NaOH, followed by coupling with S7 analogously to the procedure provided for example 1. MS (ESI) m/z 1166.9 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.42 (s, 2H), 8.07 (d, J = 9.4 Hz, 1H), 8.01 (d, J = 2.7 Hz, 1H), 7.89 (d, J = 9.7 Hz, 1H), 7.44 (t, J = 59.7 Hz, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 9.7 Hz, 1H), 6.85 (d, J = 2.7 Hz, 1H), 4.90 - 4.83 (m, 2H), 4.74 - 4.68 (m, 3H), 4.21 (d, J = 10.0 Hz, 1H), 4.11 - 3.98 (m, 4H), 3.85 (d, J = 13.0 Hz, 1H), 3.57 (s, 3H), 3.41 - 3.31 (m, 2H), 2.86 - 2.75 (m, 3H), 2.73 - 2.61 (m, 1H), 2.19 - 2.01 (m, 2H), 1.93 - 1.82 (m, 2H), 1.64 - 1.51 (m, 1H), 1.10 (s, 3H), 1.07 (s, 3H), 1.07 (s, 3H), 0.94 (s, 3H), 0.90 - 0.83 (m, 1H), 0.79 - 0.62 (m, 2H). ¹⁹F NMR (377 MHz, Methanol-d₄) δ -77.41, -77.71, -77.73, -96.95 (dd, J = 59.9, 20.5 Hz), -114.88.

**EXAMPLE 222**

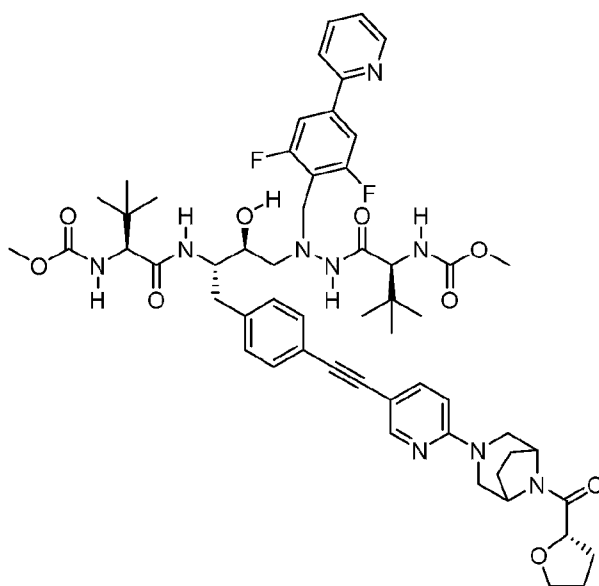
Methyl ((5S,8S,11S,12S,17S)-8-(tert-butyl)-14-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-12-hydroxy-5-isopropyl-18,18-dimethyl-11-(4-((2-(6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,9,16-tetraoxo-2-oxa-4,7,10,14,15-pentaazanonadecan-17-yl)carbamate (222). MS (ESI) m/z 1147.4 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.50 (s, 2H), 7.87 (d, J = 9.2 Hz, 1H), 7.64 (d, J = 2.4 Hz, 1H), 7.50 (d, J = 9.4 Hz, 1H), 7.35 - 7.24 (m, 4H), 7.16 (d, J = 8.0 Hz, 2H), 6.65 (d, J = 2.5 Hz, 1H), 6.13 (tt, J = 55.3, 3.9 Hz, 1H), 4.58 - 4.44 (m, 4H), 4.39 (s, 0H), 4.16 (d, J = 9.2 Hz, 1H), 4.07 - 3.92 (m, 2H), 3.90 - 3.77 (m, 2H), 3.67 (s, 1H), 3.59 (s, 1H), 3.55 (s, 3H), 3.55 (s, 3H), 2.90 - 2.66 (m, 3H), 2.06 - 1.86 (m, 2H), 0.85 (s, 9H), 0.79 (d, J = 6.8 Hz, 3H), 0.76 (s, 9H), 0.72 (d, J = 6.8 Hz, 3H). ¹⁹F NMR (377 MHz, Methanol-d₄) δ -77.64, -115.17, -125.29 (dt, J = 55.2, 14.2 Hz).

**EXAMPLE 223**

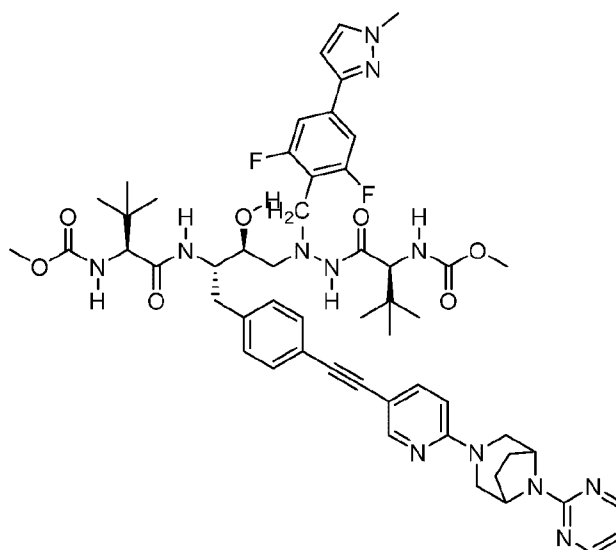
Methyl ((5S,8S,11S,12S,17S)-5,8-di-tert-butyl-14-(4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-12-hydroxy-18,18-dimethyl-11-(4-((2-(6-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyrimidin-5-yl)ethynyl)benzyl)-3,6,9,16-tetraoxo-2-oxa-4,7,10,14,15-pentaazanonadecan-17-yl)carbamate (223). MS (ESI) m/z 1174.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.21 (d, J = 2.3 Hz, 1H), 7.87 (d, J = 9.0 Hz, 1H), 7.64 (d, J = 2.4 Hz, 1H), 7.61 (dd, J = 8.8, 2.3 Hz, 1H), 7.53 (d, J = 9.2 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.1 Hz, 1H), 7.15 (d, J = 8.1 Hz, 2H), 6.77 (d, J = 8.9 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 6.13 (tt, J = 55.3, 3.9 Hz, 1H), 4.92 - 4.83 (m, 2H), 4.74 - 4.68 (m, 2H), 4.51 (td, J = 14.3, 3.9 Hz, 2H), 4.26 (d, J = 13.7 Hz, 2H), 4.16 (d, J = 9.3 Hz, 1H), 4.09 - 3.94 (m, 3H), 3.91 (s, 1H), 3.85 (d, J = 13.1 Hz, 1H), 3.70 - 3.64 (m, 1H), 3.63 - 3.57 (m, 2H), 3.55 (s, 3H), 3.54 (s, 3H), 3.28 (d, J = 13.9 Hz, 2H), 2.89 - 2.66 (m, 4H), 2.17 - 2.08 (m, 2H), 2.02 - 1.95 (m, 2H), 0.85 (s, 9H), 0.80 (s, 9H), 0.75 (s, 9H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.71, -115.18, -125.29 (dt, J = 55.3, 14.2 Hz).

**EXAMPLE 224**

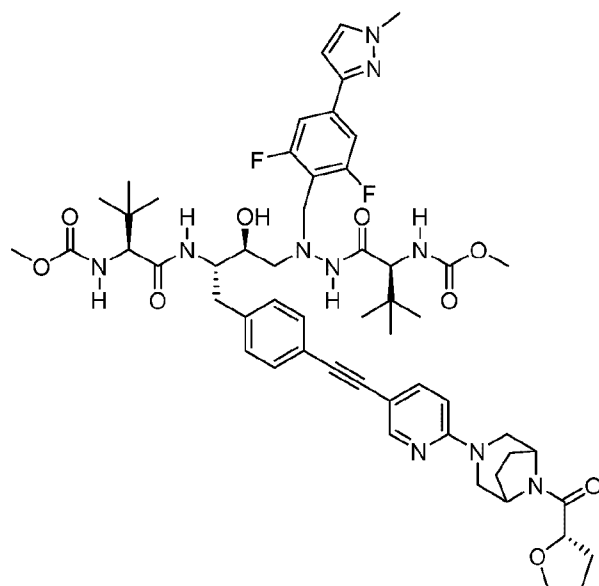
Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyridin-2-yl)benzyl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-(4-(((6-(8-((S)-tetrahydrofuran-2-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (224). Intermediates: **P28**, **I3**, and **S25**. MS (ESI) m/z 1104.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.58 (d, $J = 5.0$ Hz, 1H), 8.14 - 8.01 (m, 2H), 7.93 (t, $J = 7.7$ Hz, 1H), 7.86 (d, $J = 7.9$ Hz, 1H), 7.72 (t, $J = 8.7$ Hz, 1H), 7.50 (d, $J = 8.5$ Hz, 2H), 7.43 - 7.35 (m, 1H), 7.25 (d, $J = 7.8$ Hz, 2H), 7.14 (d, $J = 8.0$ Hz, 2H), 6.72 (d, $J = 9.8$ Hz, 1H), 4.63 - 4.54 (m, 1H), 4.39 - 4.29 (m, 1H), 4.11 - 3.73 (m, 8H), 3.66 (s, 1H), 3.59 (s, 3H), 3.53 (s, 3H), 3.13 (d, $J = 12.1$ Hz, 1H), 2.90 - 2.64 (m, 4H), 2.20 - 1.67 (m, 10H), 1.05 (s, 4H), 1.02 (s, 3H), 0.76 (s, 9H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.33, -78.06, -114.28.

**EXAMPLE 225**

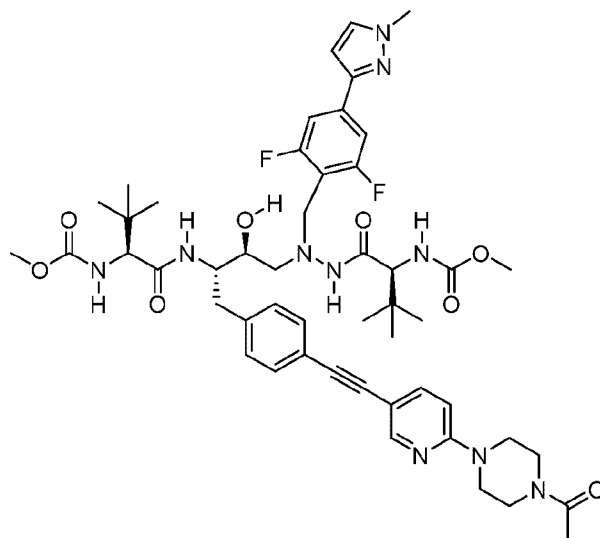
Methyl ((5S,8S,9S,14S)-5-(tert-butyl)-11-(2,6-difluoro-4-(pyridin-2-yl)benzyl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-((6-((8-((S)-tetrahydrofuran-2-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (225). Intermediates: **P28**, **I1**, and **S25**. MS (ESI) m/z 1050.4 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.67 (dt, J = 4.9, 1.4 Hz, 1H), 8.19 (d, J = 2.8 Hz, 1H), 8.00 (t, J = 7.7 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.89 - 7.74 (m, 2H), 7.59 (d, J = 8.5 Hz, 2H), 7.48 (t, J = 6.2 Hz, 1H), 7.35 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 7.8 Hz, 2H), 7.08 - 6.89 (m, 1H), 4.73 - 4.64 (m, 1H), 4.23 - 3.81 (m, 8H), 3.75 (s, 1H), 3.73 - 3.69 (m, 1H), 3.68 (s, 3H), 3.63 (s, 3H), 3.24 - 3.14 (m, 1H), 2.99 - 2.79 (m, 4H), 2.32 - 1.75 (m, 9H), 0.90 (s, 9H), 0.84 (s, 9H). ¹⁹F NMR (377 MHz, Methanol-d₄) δ -78.01, -114.33.

**EXAMPLE 226**

methyl ((5S,8S,9S,14S)-5-(tert-butyl)-11-(2,6-difluoro-4-(1-methyl-1H-pyrazol-3-yl)benzyl)-
 9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-(((6-(8-(pyrimidin-2-yl)-3,8-
 5 diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-2-oxa-4,7,11,12-
 tetraazahexadecan-14-yl)carbamate (226). Intermediates: **I1**, **P41** and **S61**. MS (ESI) m/z
 1033.4 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.31 (d, J = 4.9 Hz, 2H), 8.07 (d, J = 2.1
 Hz, 1H), 7.76 (d, J = 9.3 Hz, 1H), 7.68 (d, J = 9.1 Hz, 1H), 7.52 (d, J = 2.3 Hz, 1H), 7.29 - 7.19
 (m, 4H), 7.14 (d, J = 8.1 Hz, 2H), 6.90 (d, J = 9.3 Hz, 1H), 6.61 (t, J = 4.9 Hz, 1H), 6.56 (d, J =
 10 2.4 Hz, 1H), 4.92 - 4.84 (m, 2H), 4.08 - 3.97 (m, 2H), 3.89 (d, J = 13.0 Hz, 2H), 3.84 (s, 3H),
 3.80 (s, 1H), 3.66 (s, 1H), 3.64 - 3.59 (m, 1H), 3.58 (s, 3H), 3.56 (s, 3H), 2.87 - 2.62 (m, 3H),
 2.06 - 1.95 (m, 2H), 1.84 (q, J = 7.2, 6.6 Hz, 2H), 0.79 (s, 9H), 0.74 (s, 9H). ¹⁹F NMR (377
 MHz, Methanol-d₄) δ -77.75, -115.32.

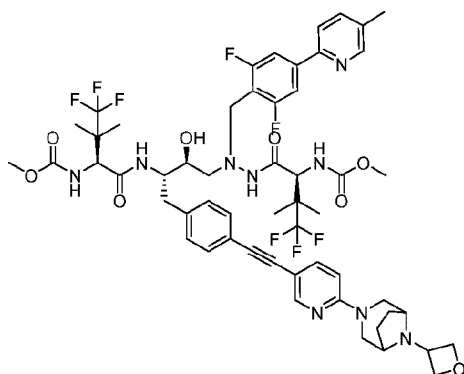
**EXAMPLE 227**

Methyl ((5S,8S,9S,14S)-5-(tert-butyl)-11-(2,6-difluoro-4-(1-methyl-1H-pyrazol-3-yl)benzyl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-(4-((6-(8-((S)-tetrahydrofuran-2-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (227). Intermediates: **I1**, **P41** and **S25**. MS (ESI) m/z 1053.3 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.10 (s, 1H), 7.79 - 7.64 (m, 2H), 7.52 (d, J = 2.3 Hz, 1H), 7.28 - 7.19 (m, 4H), 7.14 (d, J = 8.0 Hz, 2H), 6.89 (t, J = 10.6 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 4.63 - 4.55 (m, 1H), 4.09 - 3.89 (m, 3H), 3.84 (s, 3H), 3.81 - 3.73 (m, 2H), 3.66 (s, 1H), 3.64 - 3.60 (m, 1H), 3.58 (s, 3H), 3.56 (s, 3H), 3.10 (d, J = 12.2 Hz, 1H), 2.90 - 2.61 (m, 4H), 2.18 - 1.67 (m, 7H), 0.80 (s, 9H), 0.75 (s, 9H). ¹⁹F NMR (377 MHz, Methanol-d₄) δ -77.94, -115.33.

**EXAMPLE 228**

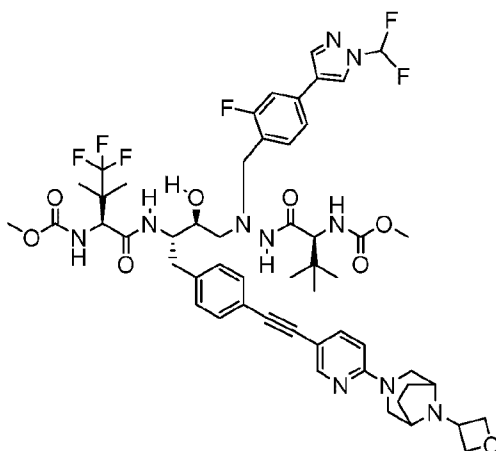
Methyl ((5S,8S,9S,14S)-8-(4-((6-(4-acetylpiperazin-1-yl)pyridin-3-yl)ethynyl)benzyl)-5-(tert-butyl)-11-(2,6-difluoro-4-(1-methyl-1H-pyrazol-3-yl)benzyl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (228).

Intermediates: **I1**, and **P41**. MS (ESI) m/z 971.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.12 (dd, $J = 2.2, 0.7$ Hz, 1H), 7.73 (d, $J = 9.4$ Hz, 1H), 7.65 (dd, $J = 9.0, 2.3$ Hz, 1H), 7.52 (d, $J = 2.3$ Hz, 1H), 7.32 - 7.18 (m, 4H), 7.14 (d, $J = 8.1$ Hz, 2H), 6.88 (d, $J = 9.2$ Hz, 1H), 4.10 - 3.97 (m, 2H), 3.90 - 3.76 (m, 5H), 3.70 - 3.50 (m, 15H), 2.90 - 2.78 (m, 2H), 2.72 (d, $J = 7.9$ Hz, 2H), 2.06 (s, 3H), 0.80 (s, 9H), 0.75 (s, 9H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.88, -115.32.

EXAMPLE 229

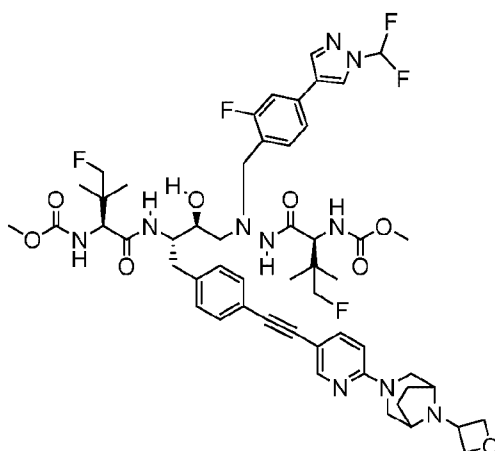
Methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(5-methylpyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)ethynyl)benzyl)-14-yl)carbamate (229).

yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (\$\$\$). Intermediates: **I2**, **P39**, **S3**. MS (ESI) m/z 1030.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.55 (s, 1H), 8.29 (d, $J = 2.2$ Hz, 1H), 8.13 (d, $J = 9.4$ Hz, 1H), 8.01 – 7.87 (m, 2H), 7.69 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.55 (d, $J = 8.4$ Hz, 2H), 7.33 (d, $J = 7.9$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 7.12 (d, $J = 9.9$ Hz, 1H), 6.86 (d, $J = 8.9$ Hz, 1H), 6.79 (d, $J = 9.9$ Hz, 1H), 4.95 (t, $J = 7.6$ Hz, 2H), 4.85 – 4.78 (m, 2H), 4.58 – 4.49 (m, 1H), 4.48 – 4.40 (m, 1H), 4.40 – 4.26 (m, 3H), 4.23 – 4.09 (m, 4H), 3.98 (d, $J = 13.1$ Hz, 1H), 3.79 – 3.71 (m, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 3.46 – 3.35 (m, 2H), 2.94 – 2.87 (m, 3H), 2.80 (t, $J = 10.9$ Hz, 1H), 2.45 (s, 3H), 2.30 – 2.19 (m, 2H), 2.12 – 2.00 (m, 2H), 1.16 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H).

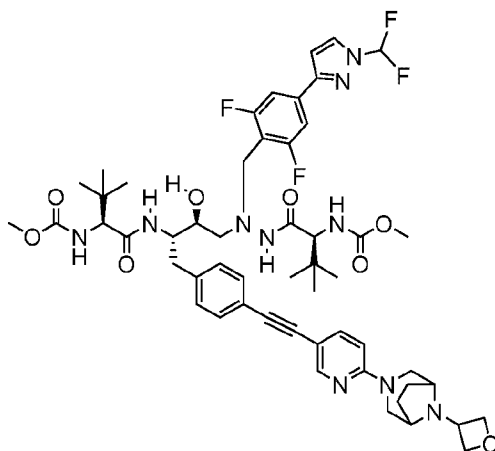


EXAMPLE 230

methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluorobenzyl)-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate. Intermediates: **I3**, **P8**, and **S3**. MS (ESI) m/z 1083.8 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.11 (d, $J = 21.6$ Hz, 4H), 7.72 – 7.55 (m, 3H), 7.42 – 7.29 (m, 5H), 7.22 (d, $J = 8.1$ Hz, 2H), 6.88 – 6.77 (m, 1H), 4.96 (t, $J = 7.6$ Hz, 2H), 4.81 (dd, $J = 8.2, 5.0$ Hz, 2H), 4.54 (s, 1H), 4.42 – 4.32 (m, 3H), 4.16 (s, 3H), 4.08 – 3.91 (m, 2H), 3.81 – 3.60 (m, 9H), 3.42 – 3.34 (m, 2H), 2.98 – 2.70 (m, 4H), 2.27 – 2.20 (m, 2H), 2.11 – 2.03 (m, 2H), 1.08 (d, $J = 22.3$ Hz, 6H), 0.80 (s, 10H).

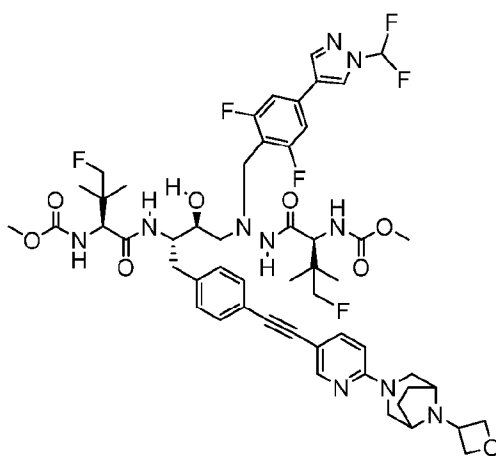
**EXAMPLE 231**

methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-fluorobenzyl)-16-
 fluoro-5-(1-fluoro-2-methylpropan-2-yl)-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-
 5 yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-2-oxa-
 4,7,11,12-tetraazahexadecan-14-yl)carbamate . Intermediates: I1a, A7, P8, and S3. MS
 (ESI) m/z 1083.8 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.48 – 8.06 (m, 3H), 7.70 (dd, J
 = 8.9, 2.3 Hz, 2H), 7.66 – 7.55 (m, 1H), 7.43 – 7.30 (m, 5H), 7.24 (d, J = 8.1 Hz, 3H), 4.96 (t, J
 = 7.6 Hz, 2H), 4.82 (dd, J = 8.3, 5.1 Hz, 3H), 4.54 (s, 1H), 4.35 (d, J = 13.4 Hz, 2H), 4.24 – 3.89
 10 (m, 12H), 3.83 – 3.59 (m, 8H), 3.39 (d, J = 13.8 Hz, 2H), 3.00 – 2.72 (m, 4H), 2.28 – 2.19 (m,
 2H), 2.12 – 2.00 (m, 2H), 0.92 – 0.75 (m, 13H).

**EXAMPLE 232**

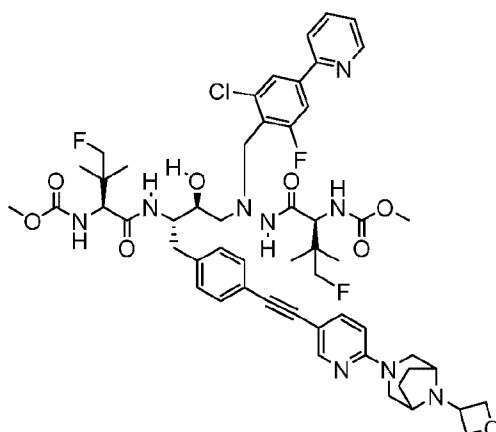
15 methyl ((5S,8S,9S,14S)-5-(tert-butyl)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-

difluorobenzyl)-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate. Intermediates: **I1**, **P4**, and **S3**. MS (ESI) m/z 1047.5 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.30 – 8.26 (m, 1H), 8.09 (d, J = 2.7 Hz, 1H), 7.80 (d, J = 9.4 Hz, 1H), 7.68 (dd, J = 9.0, 2.5 Hz, 2H), 7.48 – 7.31 (m, 5H), 7.23 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 2.8 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 4.94 (t, J = 7.5 Hz, 2H), 4.46 (s, 1H), 4.30 (d, J = 13.8 Hz, 2H), 4.18 – 4.02 (m, 5H), 4.02 – 3.88 (m, 3H), 3.79 – 3.63 (m, 9H), 3.35 (d, J = 13.7 Hz, 2H), 2.98 – 2.77 (m, 5H), 2.24 – 2.16 (m, 2H), 2.04 (d, J = 8.4 Hz, 2H), 0.87 (d, J = 21.8 Hz, 19H).

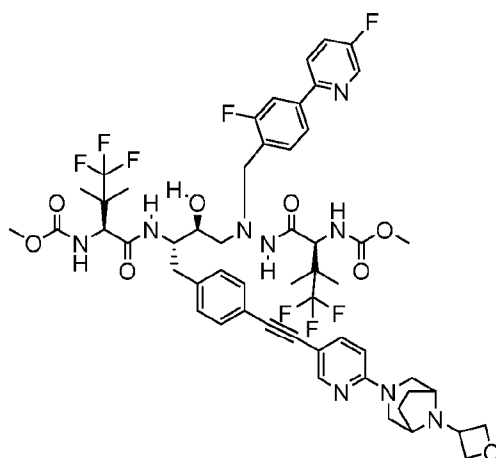


EXAMPLE 233

methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2,6-difluorobenzyl)-16-fluoro-5-(1-fluoro-2-methylpropan-2-yl)-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate. Intermediates: **I1a**, **A7**, **P7**, and **S3**. MS (ESI) m/z 1084.0 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.31 – 8.28 (m, 1H), 8.12 (s, 1H), 7.88 (d, J = 9.4 Hz, 1H), 7.70 (dd, J = 8.8, 2.3 Hz, 1H), 7.37 – 7.21 (m, 7H), 6.86 (d, J = 8.9 Hz, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.81 (dd, J = 8.0, 5.2 Hz, 3H), 4.52 (s, 1H), 4.35 (d, J = 14.0 Hz, 2H), 4.25 – 3.89 (m, 13H), 3.67 (d, J = 8.3 Hz, 8H), 3.37 (d, J = 13.8 Hz, 2H), 2.95 – 2.78 (m, 4H), 2.26 – 2.19 (m, 2H), 2.07 (d, J = 8.6 Hz, 2H), 0.95 – 0.83 (m, 13H).

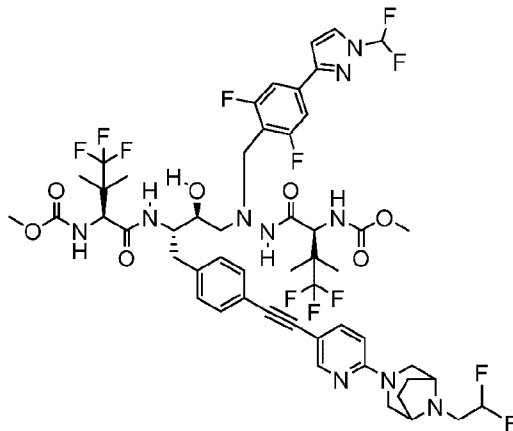
**EXAMPLE 234**

- 5 **methyl ((5S,8S,9S,14S)-11-(2-chloro-6-fluoro-4-(pyridin-2-yl)benzyl)-16-fluoro-5-(1-fluoro-2-methylpropan-2-yl)-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-**
diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-2-oxa-4,7,11,12-
tetraazahexadecan-14-yl)carbamate. Intermediates: **11a**, **A7**, **P26**, and **S3**. MS (ESI) m/z
 1060.3 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.65 (d, J = 4.8 Hz, 1H), 8.31 – 8.28 (m,
 10 1H), 7.91 (q, J = 13.2, 11.5 Hz, 4H), 7.73 – 7.65 (m, 2H), 7.34 (d, J = 7.9 Hz, 2H), 7.24 (d, J =
 8.0 Hz, 2H), 4.96 (t, J = 7.6 Hz, 2H), 4.81 (dd, J = 8.3, 5.0 Hz, 3H), 4.52 (s, 1H), 4.35 (d, J =
 14.1 Hz, 2H), 4.30 – 3.96 (m, 12H), 3.73 (s, 1H), 3.66 (d, J = 16.2 Hz, 6H), 3.38 (d, J = 13.8 Hz,
 2H), 2.99 – 2.78 (m, 5H), 2.23 (d, J = 10.7 Hz, 2H), 2.07 (d, J = 8.7 Hz, 2H), 0.93 – 0.81 (m,
 13H).

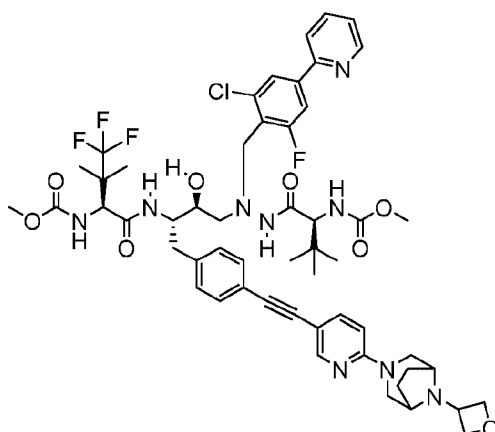


EXAMPLE 235

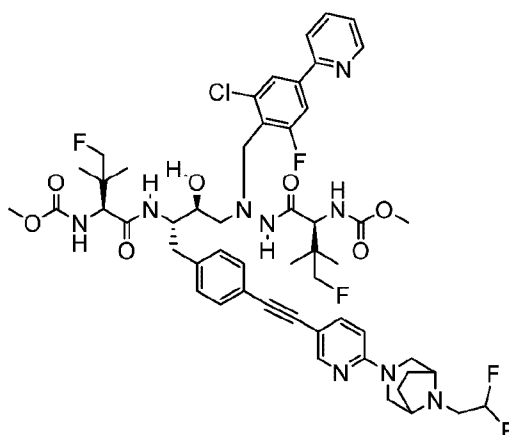
methyl ((5S,8S,9S,14S)-16,16,16-trifluoro-11-(2-fluoro-4-(5-fluoropyridin-2-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate. Intermediates: **I2**, **P14**, and **S3**. MS (ESI) m/z 1116.4 [M+H]⁺.

**EXAMPLE 236**

methyl ((5S,8S,9S,14S)-8-(4-((6-(8-(2,2-difluoroethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-11-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2,6-difluorobenzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate. Intermediates: **P4**, **A3**, and **S63**. MS (ESI) m/z 1078.4 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.29 – 8.24 (m, 1H), 8.18 – 8.08 (m, 2H), 7.74 – 7.61 (m, 3H), 7.59 – 7.51 (m, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.39 – 7.31 (m, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 2.7 Hz, 1H), 6.88 (d, J = 8.9 Hz, 1H), 4.33 – 4.28 (m, 1H), 4.27 – 4.10 (m, 7H), 3.95 (d, J = 13.2 Hz, 1H), 3.68 (d, J = 10.7 Hz, 10H), 3.42 (d, J = 13.5 Hz, 2H), 2.95 – 2.73 (m, 4H), 2.29 (d, J = 10.5 Hz, 2H), 2.08 (d, J = 8.6 Hz, 2H), 1.20 – 1.08 (m, 10H), 1.03 (s, 3H).

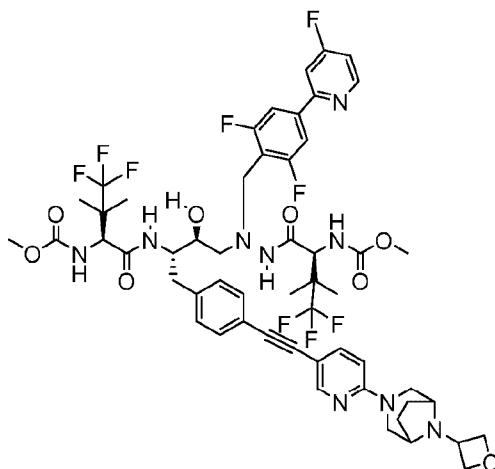
**EXAMPLE 237**

methyl ((5S,8S,9S,14S)-11-(2-chloro-6-fluoro-4-(pyridin-2-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate. Intermediates: **I3**, **P26**, and **S3**. MS (ESI) m/z 1060.3 $[M+H]^+$. 1H NMR (400 MHz, Me₂SO- d_6) δ 8.65 (d, J = 4.8 Hz, 1H), 8.12 (d, J = 9.4 Hz, 1H), 7.92 (dd, J = 18.0, 8.2 Hz, 3H), 7.73 – 7.65 (m, 2H), 7.42 (t, J = 5.5 Hz, 1H), 7.33 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.9 Hz, 1H), 4.96 (t, J = 7.6 Hz, 2H), 4.81 – 4.76 (m, 3H), 4.46 – 4.23 (m, 5H), 4.18 – 4.03 (m, 5H), 3.68 (s, 5H), 3.62 (s, 3H), 3.37 (d, J = 14.0 Hz, 3H), 2.96 – 2.75 (m, 4H), 2.23 (d, J = 10.2 Hz, 2H), 2.08 (d, J = 8.7 Hz, 2H), 1.12 (d, J = 16.0 Hz, 7H), 0.84 (s, 10H).

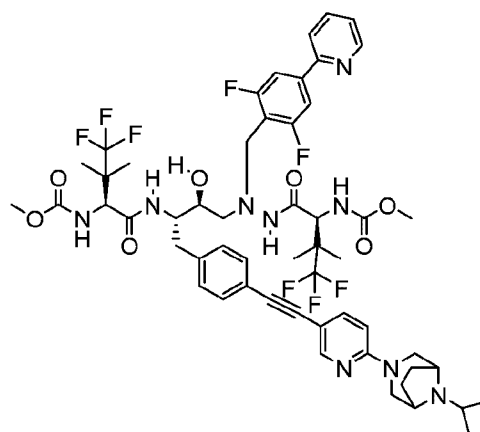


EXAMPLE 238

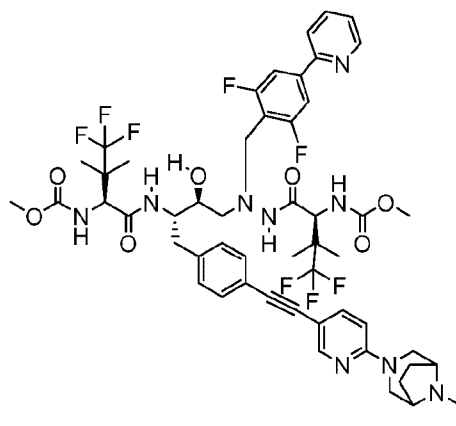
methyl ((5S,8S,9S,14S)-11-(2-chloro-6-fluoro-4-(pyridin-2-yl)benzyl)-8-((6-(8-(2,2-difluoroethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-16-fluoro-5-(1-fluoro-2-methylpropan-2-yl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate. Intermediates: **I1a**, **A7**, **P26**, and **S63**. MS (ESI) m/z 1068.6 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.65 (d, $J = 4.9$ Hz, 1H), 8.28 – 8.24 (m, 1H), 8.00 – 7.82 (m, 4H), 7.75 – 7.65 (m, 2H), 7.47 – 7.41 (m, 1H), 7.34 (d, $J = 7.9$ Hz, 2H), 7.24 (d, $J = 8.0$ Hz, 2H), 6.88 (d, $J = 8.9$ Hz, 1H), 4.31 – 3.95 (m, 15H), 3.66 (d, $J = 15.6$ Hz, 10H), 3.43 (d, $J = 13.4$ Hz, 2H), 2.99 – 2.79 (m, 4H), 2.34 – 2.24 (m, 2H), 2.08 (t, $J = 7.0$ Hz, 2H), 0.96 – 0.80 (m, 14H).

**EXAMPLE 239**

methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(4-fluoropyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate. Intermediates: **I2**, **P15**, and **S3**. MS (ESI) m/z 1134.4 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ 8.65 (dd, $J = 8.6, 5.6$ Hz, 1H), 8.29 (d, $J = 2.2$ Hz, 1H), 8.12 (d, $J = 9.5$ Hz, 1H), 7.78 – 7.61 (m, 5H), 7.33 (d, $J = 7.8$ Hz, 2H), 7.25 – 7.18 (m, 3H), 6.85 (d, $J = 8.9$ Hz, 1H), 4.96 (t, $J = 7.6$ Hz, 2H), 4.53 (s, 1H), 4.44 (d, $J = 9.7$ Hz, 1H), 4.33 (dd, $J = 19.5, 12.0$ Hz, 4H), 4.17 (d, $J = 14.3$ Hz, 5H), 3.98 (d, $J = 13.1$ Hz, 1H), 3.67 (d, $J = 16.2$ Hz, 8H), 3.38 (d, $J = 13.8$ Hz, 2H), 2.96 – 2.75 (m, 5H), 2.23 (d, $J = 11.2$ Hz, 2H), 2.08 (d, $J = 8.6$ Hz, 2H), 1.18 – 1.10 (m, 10H), 1.03 (s, 3H).

**EXAMPLE 240**

- 5 **methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-8-(4-((6-(8-isopropyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate.** Intermediates: **I2**, **P28**, and **S22**. MS (ESI) m/z 1102.1 $[M+H]^+$.

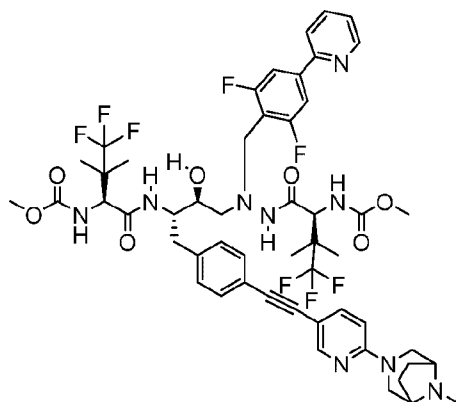


10

EXAMPLE 241

- 15 **methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyridin-2-yl)benzyl)-8-(4-((6-(8-ethyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate.** Intermediates: **I2**, **P28**, and **S21**. MS (ESI) m/z 1088.1

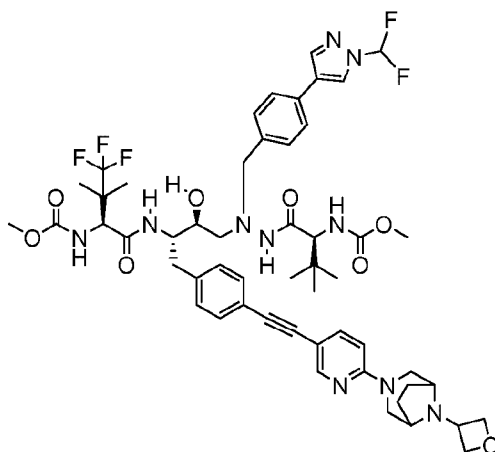
[M+H]⁺.



5

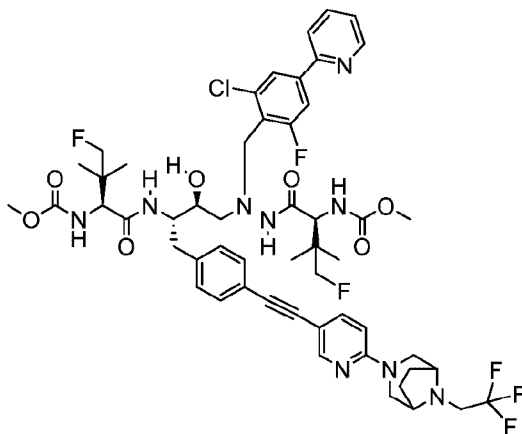
EXAMPLE 242

methyl ((5S,8S,9S,14S)-11-(2,6-difluoro-4-(pyridin-2-yl)benzyl)-16,16,16-trifluoro-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate. Intermediates: **I2**, **P28**, and **S20**. MS (ESI) m/z 1074.4 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.65 (d, J = 5.1 Hz, 1H), 8.29 (s, 1H), 7.92 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 8.9 Hz, 1H), 4.44 (d, J = 9.7 Hz, 1H), 4.33 (dd, J = 19.0, 11.6 Hz, 3H), 4.20 – 4.06 (m, 5H), 3.98 (d, J = 13.0 Hz, 1H), 3.66 (d, J = 21.3 Hz, 8H), 3.26 (s, 1H), 2.91 (d, J = 7.9 Hz, 7H), 2.31 (s, 2H), 2.07 (d, J = 8.8 Hz, 2H), 1.19 – 1.10 (m, 11H), 1.03 (s, 3H).



EXAMPLE 243

methyl ((5S,8S,9S,14S)-11-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-(4-((6-(8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate. Intermediates: **I3**, **P9**, and **S3**. MS (ESI) m/z 1065.6 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.39 – 8.28 (m, 2H), 8.08 (d, J = 26.3 Hz, 2H), 7.70 (dd, J = 8.8, 2.3 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.48 (s, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.88 – 6.73 (m, 2H), 4.96 (t, J = 7.6 Hz, 2H), 4.81 (dd, J = 8.2, 5.0 Hz, 2H), 4.52 (s, 1H), 4.37 (t, J = 13.2 Hz, 3H), 4.15 (s, 3H), 3.95 (t, J = 10.7 Hz, 2H), 3.78 (d, J = 9.5 Hz, 1H), 3.69 (d, J = 10.5 Hz, 5H), 3.62 (s, 3H), 3.38 (d, J = 13.9 Hz, 2H), 2.90 (t, J = 7.0 Hz, 2H), 2.79 (t, J = 11.1 Hz, 2H), 2.23 (d, J = 11.0 Hz, 2H), 2.07 (d, J = 8.6 Hz, 2H), 1.09 (s, 3H), 1.01 (s, 3H), 0.76 (s, 10H).



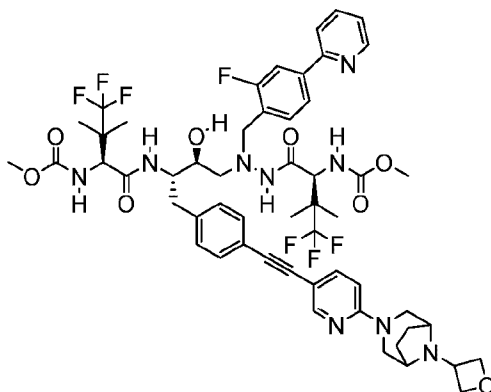
15

EXAMPLE 244

methyl ((5S,8S,9S,14S)-11-(2-chloro-6-fluoro-4-(pyridin-2-yl)benzyl)-16-fluoro-5-(1-fluoro-2-methylpropan-2-yl)-9-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-(4-((6-(8-(2,2,2-trifluoroethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate. Intermediates: **I1a**, **A7**, **P26**, and **S62**. MS (ESI) m/z 1086.4 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.67 – 8.62 (m, 1H), 7.99 – 7.80 (m, 5H), 7.71 – 7.61 (m, 2H), 7.59 – 7.51 (m, 1H), 7.44 (dd, J = 7.1, 5.1 Hz, 1H), 7.36 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 4.30 – 3.96 (m, 10H), 3.90 (d, J = 9.1 Hz, 1H), 3.84 (d, J = 11.5 Hz, 2H), 3.77 – 3.46 (m, 10H), 3.23 – 3.11 (m, 3H), 2.99 – 2.80 (m, 5H), 2.08 – 1.98 (m,

25

3H), 1.78 (t, J = 7.1 Hz, 2H), 0.95 – 0.80 (m, 12H).



EXAMPLE 245

5 **Methyl ((5S,8S,9S,14S)-16,16,16-trifluoro-11-(2-fluoro-4-(pyridin-2-yl)benzyl)-9-hydroxy-15,15-dimethyl-8-((6-((8-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)ethynyl)benzyl)-3,6,13-trioxo-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamate (ABC).** Intermediates: **I2**, **P29**, and **S3**. MS (ESI) m/z 1098.7 [M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 8.65 – 8.61 (m, 1H), 8.29 (d, J = 2.3 Hz, 1H), 8.11 (d, J = 9.1 Hz, 1H), 7.92 (dd, J = 18.5, 7.8 Hz, 2H), 7.75 – 7.62 (m, 4H), 7.33 (d, J = 7.8 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 9.9 Hz, 1H), 6.85 (d, J = 8.9 Hz, 1H), 4.96 (t, J = 7.6 Hz, 3H), 4.82 – 4.76 (m, 2H), 4.53 – 4.12 (m, 10H), 3.99 (d, J = 13.7 Hz, 3H), 3.76 (s, 1H), 3.68 (s, 3H), 3.58 (s, 3H), 3.37 (d, J = 14.0 Hz, 2H), 2.86 (dd, J = 31.3, 7.8 Hz, 4H), 2.22 (d, J = 10.8 Hz, 2H), 2.07 (d, J = 8.8 Hz, 2H), 1.18 – 1.05 (m, 9H), 0.94 (s, 3H).

15

4. Biological Assays

MT-4 HIV Assay.

Compounds were tested in a high-throughput 384-well assay format for their ability to inhibit the replication of HIV-1 (IIIB) in MT-4 cells. Compounds were serially diluted (1:3) in DMSO on 384-well polypropylene plates and further diluted 200-fold into complete RPMI media (10% FBS, 1% P/S) using the Biotek Micro Flow and Agilent ECHO acoustic dispenser. Each plate contained up to 8 test compounds, with negative (No Drug Control) and 5 μ M AZT positive controls. MT-4 cells were pre-infected with 10 μ L of either RPMI (mock-infected) or a fresh 1:250 dilution of an HIV-1 (IIIB) concentrated virus stock. Infected and uninfected MT-4 cells were further diluted in complete RPMI media and added to each plate using a Micro Flow

25

dispenser. After 5 days incubation in a humidified and temperature controlled incubator (37 °C), Cell Titer Glo (Promega) was added to the assay plates to quantify the amount of luciferase.

EC₅₀ and CC₅₀ values were defined as the compound concentration that causes a 50% decrease in luminescence signal, and were calculated using a sigmoidal dose-response model to generate curve fits. Data for certain compounds is reported in Table 1 below.

MT-4 HIV high resolution antiviral assay

Assay protocol is identical to that described for the MT-4 antiviral assay with the following changes: Each drug is run in 2 series of quadruplicates with different starting concentrations for each series and 19 1.5 fold dilutions performed across the plate. This results in an inhibition curve with 40 data points for each compound. Data is analyzed and Hill coefficients determined in Graph Pad Prism (San Diego, CA). EC₉₅s were determined by the formula $EC_{95} = (19)^{1/\text{hill coefficient}} \times EC_{50}$. HD values were determined for certain compounds and reported in Table 5 below as an illustrative example.

Liver Microsomal Stability Protocol

Test compounds and one control compound (verapamil) were tested in 3 different species in duplicate sets.

General conditions:

Test compound concentration: 1 uM; Protein concentration: 0.5 mg/mL (for dog, rat, and human liver microsomes); Cofactor: NADPH-Regenerating system (NRS) solution.; Time-points: 2, 12, 25, 45, and 65 minutes.

Reaction composition (in each incubation well) contains:

5	uL compound (50 uM stock solution, 50:50 ACN:H ₂ O)
25	uL NRS solution
6.25	uL 20 mg/mL liver microsomes
213.75	uL 100 mM KPO ₄ , pH 7.4

250 uL total volume

At an incubation temperature of 37°C, the reaction was started with addition of NADPH Regeneration System, at each time point, 25 uL of the reaction mixture was removed and added to a plate with 225 uL quenching solution (50 % MeOH, 25 % ACN, 25 % H₂O, and 200 nM labetalol as internal standard). After plates were vortexed, they were centrifuged for 30 minutes to remove proteins. About 100µL supernatant was removed to a new plate and diluted with

150µL water. About 20 µL of the mixture was injected into LC/MS/MS system to monitor the compound's response. In vitro measured $t_{1/2}$ was used to calculate Clint values. Data is presented in Table 1 below and Figure 1.

5

TABLE 1

Cmpd	EC₅₀ (nM)	Rat. Pred. Cl. (L/H/kg)	Dog. Pred. Cl. (L/H/kg)	Human Pred Cl. (L/H/kg)
1	-	-		-
2	2.64			
3	6.95			
4	2.82			
5	4.37			
6	3.56	0.22		<0.11
7	3.61	0.21		<0.11
8	2.46			
9	10.13			
10	3.46			
11	3.72	0.18		0.18
12	3.11			
13	6.3			
14	4.39	1.13		0.66
15	4.22			

16	4.64	0.45		<0.11
17	7.24			
18	5	1.03		0.13
19	8.43	0.29		<0.11
20	4.39	0.18		0.34
21	2.32			
22	3.24			
23	4.82	0.22	0.21	<0.11
24	3.82			
25	3.19	1.41		0.16
26	4.24	1.6		<0.11
27	3.5			
28	4.56			
29	4.02			
30	4.44			
31	3.06	0.75		<0.11
32	2.65	0.59		<0.11
33	4.71			
34	5.26			
35	3.54	2.1	1.74	<0.11
36	3.68	0.27		<0.11
37	6.75	0.32		<0.11

38	6.13			
39	2.57	0.54		0.15
40	3.89	0.5		0.13
41	3.58			
42	3.18			
43	2.87	1.01	1.66	0.16
44	3.97	2.54		0.13
45	2.56	0.92		<0.11
46	4.34	0.19	1.64	<0.11
47	7.18			
48	114.29	0.18		<0.11
49	37.3			
50	4.31	<0.18		<0.11
51	2.8			<0.11
52	8.15	<0.18		0.14
53	2.98	0.2		0.51
54	8.47			
55	4.44			
56	3.59	0.19	1.47	0.17
57	2.91	<0.18		<0.11
58	4.79	0.24		<0.11
59	3.38	0.83		0.6

60	3.42	0.65		0.12
61	4.11	<0.18		<0.11
62	8.83			
63	4.25	0.2	0.86	<0.11
64	5.4			
65	7.7			
66	14.52			
67	6.25	1.43		0.41
68	7.25	0.61		<0.11
69	3.24	<0.18		<0.11
70	4.79	<0.18		<0.11
71	3.37	<0.18	0.47	<0.11
72	5.19	<0.18		0.14
73	4.72	<0.18		0.13
74	6.79	0.2	1.53	0.17
75	3.41	0.21		<0.11
76	3.53			
77	2.49	0.25		<0.11
78	6.27	<0.18		<0.11
79	3.53	<0.18		<0.11
80	3.13			
81	4.39	0.39		<0.11

82	4.4	0.44		0.82
83	17.25			
84	3.23			
85	3.78	0.19		0.13
86	2.61	<0.18		<0.11
87	4.26	0.23		0.13
88	4.57	<0.18	1.63	<0.11
89	3.32	<0.18	1.67	<0.11
90	3.45	0.67		0.14
91	3.69			
92	3.72			
93	2.49	1.13		0.19
94	2.57			
95	2.44	1.39		0.38
96	2.33			
97	4.54	0.31		0.46
98	4.97	0.65		0.26
99	7.96	0.26		<0.11
100	7.96			
101	4.22	<0.18		<0.11
102	5.68	<0.18		0.18
103	4.84	0.32		0.16

104	4.97			
105	3.16			0.39
106	4.04			
107	2.23			1.1
108	7.23			
109	59.71			
110	30.8			
111	7.22			
112	4.45	0.32		<0.11
113	6.01			
114	5.1	0.28		<0.11
115	3.19	<0.18		0.12
116	2.79	0.39		0.19
117	4.15			
118	10.61			
119	3.66	0.27	1.35	<0.11
120	5.36	0.53		0.14
121	3.31	<0.18		<0.11
122	4.57			<0.11
123	4.16	<0.18		<0.11
124	6.32	0.5		<0.11
125				

126	4.13	<0.18		0.45
127	4.19	1.3		0.54
128	3.16	0.37		0.15
129	3.62			<0.11
130	3.41	<0.18		0.32
131	5.24			<0.11
132	18.24			
133	3.44	<0.18		<0.11
134	5.52	<0.18		<0.11
135	3.64			
136	3.85			
137	3.31			
138	2.32	0.95		0.17
139	3.92			
140	5.09			
141	6.68			
142	8.78			
143	7.79			
144	5.12			0.95
145	5.06			<0.11
146	8.17			<0.11
147	6.79			<0.11

148	6.95			
149	8.3			
150	5.86			
151	4.82			
152	6.16			
153				
154	4.81	<0.18		<0.11
155	8.95			
156	17.04			
157	4.53			
158	4.37	0.22		<0.11
159	3.83			<0.11
160	5700			
161	14			<0.11
162	12.25			
163	2.32			<0.11
164	7.89			
165	4.05	3.2		0.56
166	7.06			
167	4.97			<0.11
168	5.48	2.42		0.19
169	6.76			

170	4.13	<0.18		<0.11
171	4.59	0.215	0.27	<0.11
172	5.86			
173	2.55	1.2		<0.11
174	2.33	0.69		0.18
175	2.17	0.7		0.67
176	3.36	0.75		<0.11
177	8.12			
178	10.32			
179	3.55	0.27		0.33
180	3.69	<0.18		<0.11
181	8.5			
182	8.82			
183		-		-
184	3.66	<0.18		<0.11
185	2.58	0.31		0.32
186	4.74			<0.11
187	4.7			
188	9			
189	5.47			
190	7.06			
191	17.42			

192	2.89	0.36	1.04	0.22
193	2.78			
194	7.2			
195	2.76	0.52		0.12
196	10.54			
197	2.61	0.32		<0.11
198	2.19	0.33		<0.11
199	2.72	0.48	0.91	<0.11
200	4.36	0.19		<0.11
201	2.67	0.49		0.27
202	9.67			
203	5.02	1.09		0.32
204	3.18	0.48		0.19
205	5.25			
206	3.7	1.03		0.41
207	2.46	0.92		0.25
208	2.51	0.74		0.16
209	3.19	1.21		1.12
210	14.98	<0.18		0.18
211	5.75			
212	4.97	0.33		0.33
213	4.86			

214	12.33	<0.18		<0.11
215	18.21			
216	114.29			
217	113.31			
218	2.99	0.45		0.92
219	4.1	0.24	0.19	<0.11
220	7.66	0.34	0.46	<0.11
221	4.49	0.28	0.14	<0.11
222	12.93			
223	12.88			
224	4.12			
225	4.26			
226	14.93			
227	2.9			
228	1.66			
229	7.86	0.26		<0.11
230	3.97			
231	2.77			
232	2.47			
233	2.71	<0.18		<0.11
234	2.54			
235	16.74			

236	37.03			
237	4.89			
238	12.3			
239	4.45	<0.18		<0.11
240	5.62			
241	6.57			
242	3.45			
243	5.32			
244	19.53			
245	3.59			
DRV		2.8	1.2	1.2
ATV		3.7	1.4	1.07

3H Human Predicted Clearance Assay:

For certain compounds, tritiated analogs (H^3) were prepared to further determined their human predicted clearance with increased resolution. Those studies were performed as described above
 5 using the tritiated analogs. Data from those compounds is found in Table 2 below and reported in Figure 1 (note ATV and DRV were not tritiated).

Table 2

Compound	3H Human Predicted Cl.
23	0.07
36	0.1
46	0.04
51	0.11

58	0.05
88	0.08
73	0.09
75	0.11
89	0.08
101	0.08
112	0.11
153	0.43
170	0.05
171	0.02
173	0.14
176	0.09
199	0.15
208	0.11
239	0.13

Pharmacokinetic Profiling

Dog PK

- 5 Test compound was formulated in 5% EtOH, 55% PEG 300 and 40% Water (pH 2, HCl) for IV infusion administration and was formulated in 5% Ethanol, 55% PEG 300, 1% Tween™ 80 and 39% water (pH 2) for oral dosing. Each dosing group consisted of three non-naïve male beagle dogs. At dosing, the animals weighed between 9 to 12 kg. The animals were fasted overnight prior to dose administration and up to four hours after dosing. The test article was administered by intravenous infusion over 30-minutes. The rate of infusion was adjusted according to the body weight of each animal to deliver a dose of 0.5 or 1.0 mg/kg. For the oral dosing group, the test article was administered by oral gavage at a dose volume of 2 mL/kg.
- 10

Serial venous blood samples (approximately 1.0 mL each) were collected at predose and 0.25, 0.48, 0.58, 0.75, 1.0, 1.5, 2, 4, 8, 12 and 24 hours post dose from each animal for the IV dosing group; blood samples were collected at predose, 0.25, 0.50, 1, 2, 4, 6, 8, 12 and 24 hours post dose for the oral dosing group. The blood samples were collected into Vacutainer™ tubes containing EDTA-K2 as the anti-coagulant and were immediately placed on wet ice pending centrifugation for plasma. An LC/MS/MS method was used to measure the concentration of test compound in plasma. Non-compartmental pharmacokinetic analysis was performed on the plasma concentration-time data. Data for certain compounds are reported in Figure 2 and Table 3 below. VSS = apparent volume of distribution, t_{1/2} = half life, F = oral bioavailability.

Table 3

Compound	DOG IV CL (L/HR/KG)	DOG IV VSS (L/KG)	DOG IV T_{1/2} (HR)	DOG PO F (%)	DOG PO DOSE (mg/kg)
58	0.47	6.34	13.8	18	2
63	0.28	2.4	8.16		
170	1.39	4.35	7.62	2.45	2
171	0.26	3.12	13.4	23	2
DRV	2.7	0.87	0.37	38	2
ATV	1.0	0.90	1.3	48	10

Rat PK:

- Test article was formulated in 5% Ethanol, 55% PEG 300 and 40% Water (pH 2) for IV infusion administration and was formulated in 5% Ethanol, 55% PEG 300, 1% Tween 80 and 39% water (pH 2) for oral administration. Each dosing group consisted of 3 male naïve SD Rats. At dosing, the animals weighed between 0.27 to 0.32 kg. The animals were fasted overnight prior to dose administration. The test article was administered by intravenous infusion over 30 min.
- The rate of infusion was adjusted according to the body weight of each animal to deliver a dose of 0.5 or 1.0 mg/kg. For the oral dosing group, the test article was administered to animals by oral gavage administration. Serial venous blood samples (approximately 0.30 mL each) were taken at predose and 0.25, 0.48, 0.58, 0.75, 1.5, 3, 6, 8, 12 and 24 hours post dose for the IV dosing group animals. Blood samples were taken at predose, 0.25, 0.50, 1, 2, 4, 6, 8, 12 and 24

hours post dose for the oral group animals. The blood samples were collected into Vacutainer™ tubes containing EDTA-K2 as the anti-coagulant and were immediately placed on wet ice pending centrifugation for plasma. An LC/MS/MS method was used to measure the concentration of test compound in plasma. Non-compartmental pharmacokinetic analysis was performed on the plasma concentration-time data.

Data for certain compounds are reported in Table 4 and Figure 3 accordingly.

Table 4

Compound	RAT IV CL (L/HR/KG)	RAT IV VSS (L/KG)	RAT IV T1/2 (HR)	RAT PO F (%)	RAT PO DOSE (mg/kg)
36	0.32	5.99	15.7	16.4	2.5
46	0.45	4.22	9.22	13	2.5
56	0.85	7.44	8.77	34.1	2.5
57	0.36	2.45	6.28	23.2	2.5
58	0.48	6.68	12.8	37.2	2.5
61	0.43	6.5	12.9	18.5	2.5
63	0.42	5.46	11.9	19	2.5
71	0.9	7.26	9.27	24.6	2.5
73	0.32	3.34	9.43	35	2.5
74	0.39	5.07	11.6	35.8	2.5
79	0.77	4.07	5.13	13.1	2.5
89	0.3	3.53	10.2	44.2	2.5
101	0.48	6.07	10	38.4	2.5
130	0.39	5.27	11.5	55.7	2.5
170	0.35	3.32	9.38	36.6	2.5
171	0.32	8.11	22.5	39	2.5

180	0.39	0.52	2.81	4.29	2.5
199	0.46	1.07	2.09	14.7	2.5
221	0.32	4.41	11.5	19.9	2.5
239	0.4	5.49	12.9	26.3	2.5
DRV	2.2	0.73	0.32	24	2.0
ATV	2.7	0.87	0.37	38	5.0

Protease Resistance Screening.

Drug EC₅₀ values versus PI resistant mutant viruses for certain compounds were determined in a 5-day multi-cycle cell viability assay measuring protection from cytopathic effect (CPE). Briefly, MT-2 cells were bulk infected at a density of 2×10^6 cells/mL with WT or mutant viruses at a multiplicity of infection (MOI) of 0.01 by gently rocking the culture for 3 hours at 37°C and then added in triplicate to 96-well plates (Corning Life Sciences, Tewksbury, MA, USA). Cells were incubated in complete RPMI medium containing a 10-point, 3-fold serial drug dilution (0.5% final DMSO concentration) for five days at 37°C in 5% CO₂. After this time, 100 µL of CellTiter-Glo reagent (Promega, Madison, WI, USA) was added to each well and the luminescence signals quantified on an EnVision plate reader (Perkin-Elmer, Inc., Waltham, MA, USA). EC₅₀ values, defined as the drug concentration inducing a 50% protection from HIV-induced cell killing, were calculated from a minimum of three independent experiments performed in quadruplicate using XLFit™ software (IDBS, Ltd., Guildford, Surrey, UK) and nonlinear regression analysis. As an illustrative example, data associated with the compound of Example 58 (GSPI1) is presented in Figure 4 below as compared to other HIV protease inhibitors (atazanavir and darunavir).

MT- 2 cell viral breakthrough assay.

MT-2 cells were infected with HIV-1_{MB} (Advanced Biotechnologies, Eldersburg, MD, USA) at a relatively high multiplicity of infection (MOI=0.05) for 3 hours and plated in 24-well plates at 2×10^5 cells per well. Drugs were added 16 hours later to a minimum of quadruplicate wells at fixed multiples of their EC₅₀ values. Every 3-4 days, cells were diluted (1:5) into freshly prepared cell culture media containing drug concentrations at the same multiple of EC₅₀ values and monitored for virus-induced cytopathic effects (CPE) over a period of 32 days. Cell-free

viral supernatants were harvested from wells showing >80% CPE and kept frozen at -80°C until further analyzed. As an illustrative example, data associated with the compound of Example 58 (GSPII) is presented in Figure 5 below as compared to other HIV protease inhibitors (atazanavir, darunavir) and efavirenz.

5 **Genotypic analysis of breakthrough viruses.**

Total RNA was purified from the cell-free supernatants obtained from each CPE-positive and p24-positive well using the Qiagen Viral RNA Isolation kit (Qiagen, Valencia, CA, USA). The coding regions targeted by each drug were amplified by One-Step RT-PCR (Qiagen) and the products subjected to DNA sequencing. Sequence changes were identified by alignment with
10 input virus sequences using Sequencher (Gene Codes Corp., Ann Arbor, MI, USA) and amino acid substitutions determined.

Equilibrium dialysis assay

Pooled plasma (from at least 3 males and 3 females) was from Bioreclamation IVT. Sodium EDTA was used as the anticoagulant. 10% plasma was diluted in 0.133M phosphate buffer
15 consisted of 1.5% (w/v) Sodium EDTA.

RPMI cell culture media consisted 10%FBS was provided by biology department, Gilead Sciences, Inc.

Plasma protein binding assay: Studies were conducted in duplicate or triplicate using a Dianorm Equilibrium Dialyser (Harvard Apparatus, Holliston MA) with each cell consisting of a
20 semipermeable membrane (2.4 cm working diameter) separating two 1 mL PTFE half-cells (Weder HG, Schildknecht J, Kesselring P. A new equilibrium dialyzing system. *American Laboratory*. 1971; **10**: 15-21). Prior to the study, the dialysis membrane was soaked for approximately one hour in 0.133 M phosphate buffer, pH 7.4. 10% plasma and cell culture media spiked with 1 µM compound (1 mL) were placed into opposite sides of the assembled
25 dialysis cells and the dialysis cells were then rotated slowly in a 37°C water bath. After the equilibration period, matrix-containing samples from both sides were drained into pre-weighed polypropylene tubes. Post-dialysis 10% plasma samples were transferred into centrifuge tubes containing 1mL of blank cell culture media. Post-dialysis cell culture media samples were transferred into centrifuge tubes containing 1mL of blank 10% plasma. All samples weights
30 were measured and recorded for calculations of volume shift and recovery.

Samples were deproteinated by treatment with four volumes of 90% (v/v) acetonitrile, 10% (v/v) methanol containing the LC-MS internal standard. Samples were centrifuged 15,000 rpm at 4°C

for 15 min and 200 μ L aliquots of the supernatants removed and mixed with an equal volume of water. Samples were vortexed for 2 min, and then aliquots (10 μ L) subject to LC-MS/MS analysis.

Data analysis

- 5 The binding ratio for an analyte in plasma vs. cell culture media was calculated using the following equations:

$$\text{Ratio} = C_{10\% \text{ plasma}}/C_{\text{CCM}}$$

- where $C_{10\% \text{ plasma}}$ is the post-dialysis 10% plasma concentration (determined by PAR), and C_{CCM} is the post-dialysis cell culture media concentration (determined by PAR),
- 10 respectively. Each concentration was corrected gravimetrically for changes in liquid volume in the dialysis cells occurring during dialysis.

Protease Ki Assay

- Inhibitor potency was measured using an enzymatic assay with a fluorogenic readout. To a reaction buffer containing 100 mM ammonium acetate at pH 5.3, 100 mM
- 15 NaCl, 1 mM EDTA, 1 mM DTT, 0.25 mg/mL BSA and 1% DMSO were added 2.5 nM of recombinant HIV protease and test compound at one of various concentrations. After a 20-minute pre-incubation, the enzymatic reaction was initiated by the addition of the fluorogenic substrate (2-aminobenzoyl)Thr-Ile-Nle-(p-nitro)Phe-Gln-Arg (Bachem) to a final concentration of 40 μ M. The total volume of the assay solution was 100 μ L. The
 - 20 reaction was measured over 20 minutes on a Tecan Infinite M1000 plate reader using an excitation wavelength of 320 nm and a detection wavelength of 420 nm. The slopes of the progress curves were the measure of reaction rates. Reaction rates were plotted as a function of inhibitor concentration, and the data were fit using the tight-binding equation described by Morrison (Biochim. Biophys. Acta 1969, 185, 269-286) to yield K_i values.

25

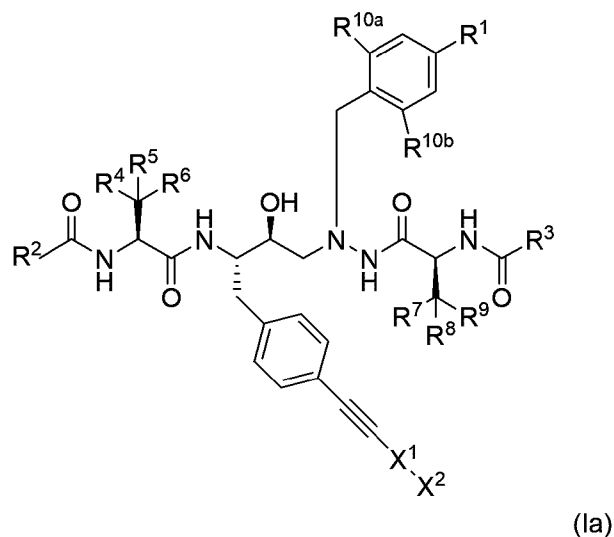
Table 5: Potency of Compound 58, DRV, and ATV

	Compound 58	darunavir	atazanavir
Ki (nM)	0.060	<0.030	0.035
EC ₅₀ (nM)	6.8	7.2	9.7
Hill-coefficient	5.8	2.9	3.1
EC ₉₅ (nM)	11.4	19.9	25

Protein Adjusted	353	42	75
EC ₉₅ (nM)			

CLAIMS

1. A compound of Formula (Ia):



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is a 5 to 10-membered heterocycle having 1 to 5 heteroatoms selected from N, O, and S, or a 5 to 10-membered heteroaryl having 1 to 5 heteroatoms selected from N, O, and S, wherein the 5 to 10-membered heterocycle or 5 to 10-membered heteroaryl is optionally substituted with 1 to 5 R^a groups;

R² and R³ are each independently C₁₋₄alkyl, C₃₋₆cycloalkyl, O-R^{2A}, C₁₋₂alkyl-O-R^{2A}, N-(R^{3A})₂, or C₁₋₂alkyl-N-(R^{3A})₂,

wherein each R^{2A} is independently C₁₋₄alkyl, C₃₋₆cycloalkyl, or a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S,

wherein each R^{3A} is independently hydrogen, C₁₋₄alkyl, C₃₋₆cycloalkyl, or COO(R^c),

and wherein each C₃₋₆cycloalkyl or 4 to 10-membered heterocyclyl is optionally substituted by 1 to 3 R^f groups, wherein each R^f is independently C₁₋₂alkyl or halogen;

R⁴ is C₁₋₄alkyl or C₁₋₄haloalkyl;

R⁷ is C₁₋₄alkyl or C₁₋₄haloalkyl;

R⁵, R⁶, R⁸, and R⁹ are each independently C₁₋₂alkyl or C₁₋₂haloalkyl;

and wherein two or more of R⁴, R⁵ and R⁶ or two or more of R⁷, R⁸, and R⁹ optionally join together to form one or more C₃₋₆cycloalkyl groups that are optionally substituted with 1 to 4 groups selected from halogen, C₁₋₂alkyl, and C₁₋₂haloalkyl;

R^{10a} and R^{10b} are halogen;

each R^a is independently halogen, C₁₋₄alkyl, C₁₋₄alkyl substituted with 1 to 2 groups selected from hydroxyl and C₁₋₄alkoxy, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₃₋₆cycloalkyl, 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S which is optionally substituted with R^{a1}, or O-R^{3B},

wherein R^{3B} is C₃₋₆cycloalkyl optionally substituted with R^{a1} or a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S optionally substituted with R^{a1},

wherein each R^{a1} is independently C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄haloalkyl, or 4 to 8-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S;

X¹ is a 6 to 10-membered aryl or a 5 to 10-membered heteroaryl having 1 to 3 heteroatoms selected from N, O, and S, wherein each 6 to 10-membered aryl or 5 to 10-membered heteroaryl is optionally substituted with 1 to 4 R^b groups;

X² is hydrogen or a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S, wherein the 4 to 10-membered heterocyclyl is optionally substituted with one R¹¹ and optionally substituted with 1 to 5 R^b groups;

R¹¹ is C=O(R^c), CH₂(R^d), S(O)₁₋₂(C₁₋₄alkyl), S(O)₁₋₂C₃₋₆cycloalkyl, a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S, or a 5 to 9-membered heteroaryl having 1 to 5 heteroatoms selected from N, O, and S, wherein each 4 to 10-membered heterocyclyl or 5 to 9-membered heteroaryl is optionally substituted with 1 to 5 R^b groups;

each R^b is independently halogen, oxo, C₁₋₄alkyl, C₁₋₄alkyl substituted with 1 to 2 groups selected from hydroxyl and C₁₋₄alkoxy, C₁₋₄haloalkyl, C₁₋₄alkoxy, or COO(R^e);

R^c is C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, N(R^e)₂, C₃₋₆cycloalkyl, or a 4 to 6-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S,

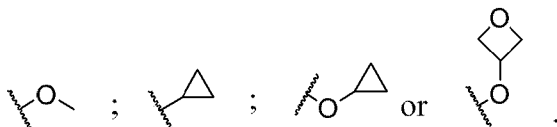
wherein the C₃₋₆ cycloalkyl and the 4 to 6-membered heterocyclyl are optionally substituted by 1 to 5 R^b groups;

R^d is COO(R^e), N(R^e)₂, C₃₋₆ cycloalkyl, or a 4 to 6-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S, wherein the C₃₋₆ cycloalkyl and the 4 to 6-membered heterocyclyl is optionally substituted by 1 to 5 R^b groups;

and each R^e is independently hydrogen or C₁₋₄alkyl.

2. The compound of claim 1, wherein R² and R³ are each independently C₁₋₄alkyl, C₃₋₆cycloalkyl, or O-R^{2A}, wherein R^{2A} is C₁₋₄alkyl, C₃₋₆cycloalkyl, or a 4 to 10-membered heterocyclyl having 1 to 5 heteroatoms selected from N, O, and S.

3. The compound of claim 1 or 2, wherein R² and R³ are each independently:



4. The compound of any one of claims 1 to 3, wherein R² and R³ are each methoxy.

5. The compound of any one of claims 1 to 4, wherein R⁴ is C₁₋₄haloalkyl.

6. The compound of any one of claims 1 to 5, wherein R⁴ is CF₃.

7. The compound of any one of claims 1 to 6, wherein R⁷ is C₁₋₄haloalkyl.

8. The compound of any one of claims 1 to 7, wherein R⁷ is CF₃.

9. The compound of any one of claims 1 to 8, wherein R⁵ and R⁶ are C₁₋₂alkyl.

10. The compound of any one of claims 1 to 9, wherein R⁵ and R⁶ are methyl.

11. The compound of any one of claims 1 to 10, wherein R⁸ and R⁹ are C₁₋₂alkyl.

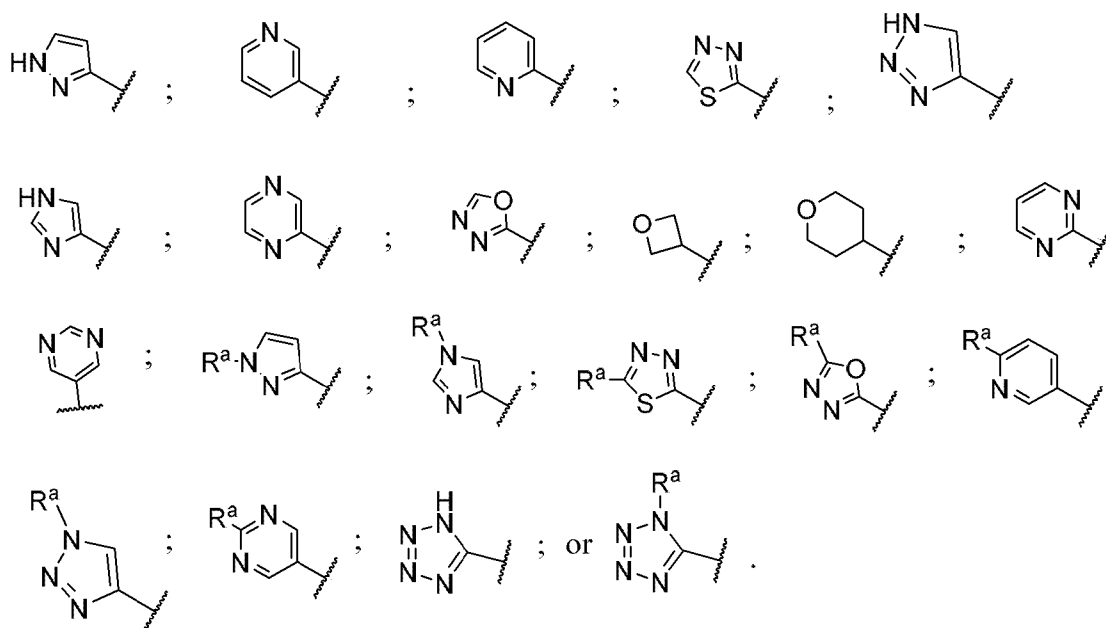
12. The compound of any one of claims 1 to 11, wherein R⁸ and R⁹ are methyl.

13. The compound of any one of claims 1 to 12, wherein R^{10a} and R^{10b} are each fluoro.

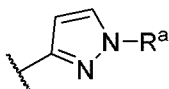
14. The compound of any one of claims 1 to 13, wherein R^1 is a 5 to 6-membered heterocycle having 1 to 3 heteroatoms selected from N, O, and S, or a 5 to 6-membered heteroaryl having 1 to 3 heteroatoms selected from N, O, and S, wherein the 5 to 6-membered heterocycle or 5 to 6-membered heteroaryl is optionally substituted with 1 to 3 R^a groups.

15. The compound of any one of claims 1 to 14, wherein R^1 is a 5 to 6-membered heterocycle having 1 to 3 heteroatoms selected from N, O, and S and is optionally substituted with 1 to 3 R^a groups.

16. The compound of any one of claims 1 to 15, wherein R^1 is independently:

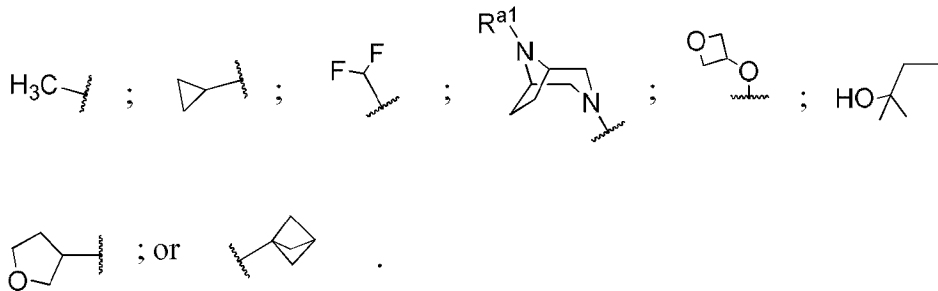


17. The compound of any one of claims 1 to 16, wherein R^1 is:



18. The compound of any one of claims 1 to 17, wherein R^a is independently C_{1-4} alkyl, C_{1-4} alkyl with 1 to 2 groups selected from hydroxyl and C_{1-4} alkoxy, or C_{1-4} haloalkyl.

19. The compound of any one of claims 1 to 17, wherein R^a is:



20. The compound of any one of claims 1 to 17, wherein R^a is C_{1-4} haloalkyl.

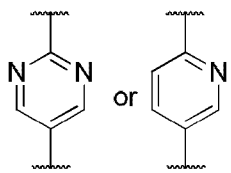
21. The compound of any one of claims 1 to 20, wherein R^a is:



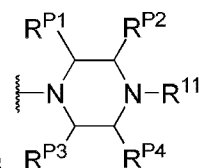
22. The compound of any one of claims 1 to 21, wherein X^1 is a 6-membered aryl or a 5 to 6-membered heteroaryl having 1 to 3 heteroatoms selected from N, O, and S, wherein each 6-membered aryl or 5 to 6-membered heteroaryl is optionally substituted with 1 to 4 R^b groups.

23. The compound of any one of claims 1 to 22, wherein X^1 is pyrimidine or pyridine.

24. The compound of any one of claims 1 to 23, wherein X^1 is:



25. The compound of any one of claims 1 to 24 wherein X^2 is a 4 to 10-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S and is optionally substituted with one R^{11} and optionally substituted with 1 to 5 R^b groups.



26. The compound of any one of claims 1 to 25, wherein X^2 is R^{P3} R^{P4} wherein:

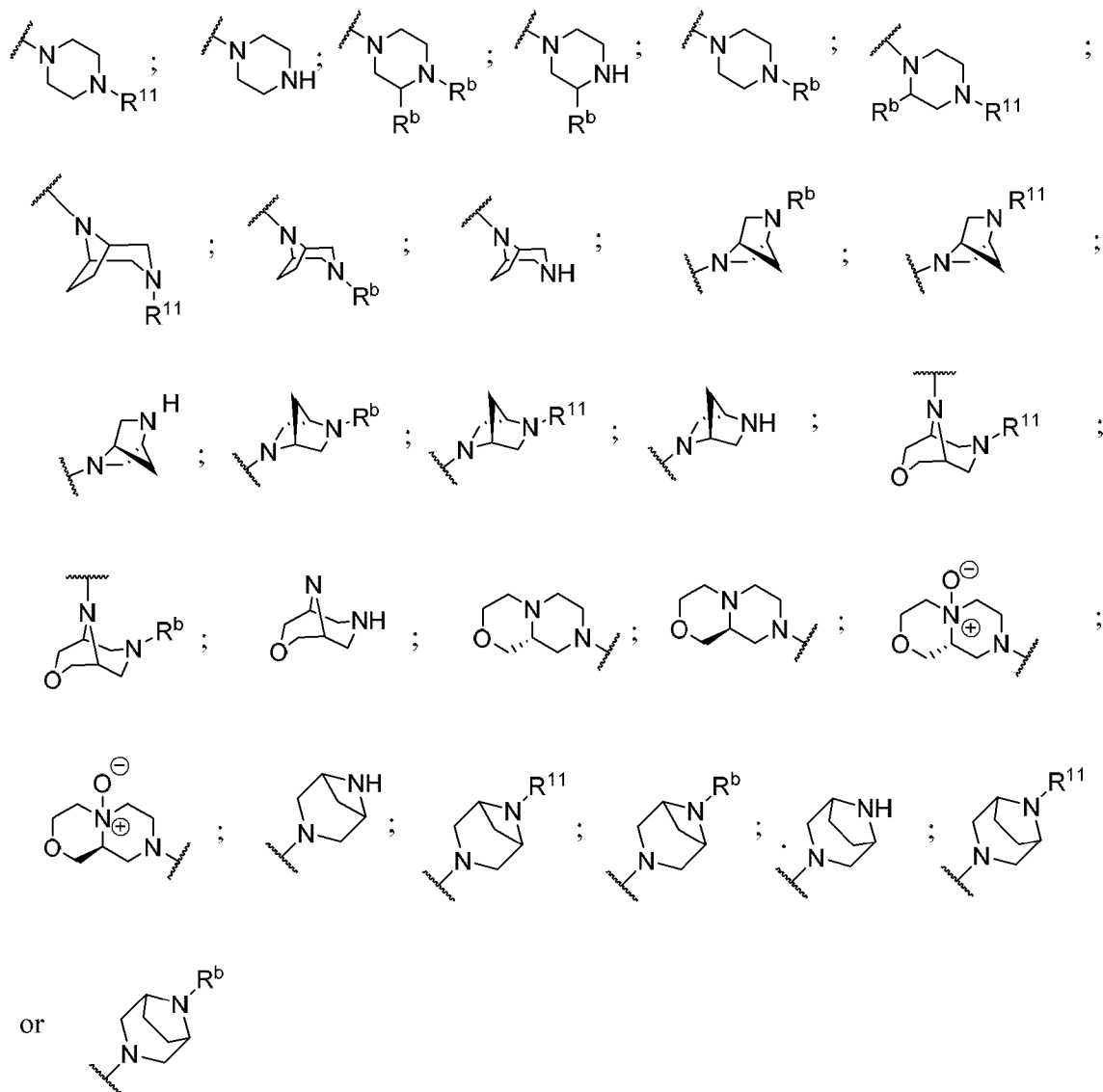
- a) R^{P1} , R^{P2} , R^{P3} , and R^{P4} are each hydrogen;
 - b) R^{P1} and R^{P3} are taken together to form a $-CH_2-$ or $-CH_2CH_2-$ group and R^{P2} and R^{P4} are each hydrogen;
 - c) R^{P2} and R^{P4} are taken together to form a $-CH_2-$ or $-CH_2CH_2-$ group and R^{P1} and R^{P3} are each hydrogen;
 - d) R^{P1} and R^{P4} are taken together to form a $-CH_2-$ group and R^{P2} and R^{P3} are each hydrogen;
- or
- e) R^{P2} and R^{P3} are taken together to form a $-CH_2-$ group and R^{P1} and R^{P4} are each hydrogen.

27. The compound of claim 26, wherein:

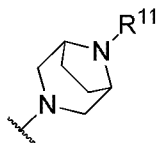
R^{P1} and R^{P3} are taken together to form a $-CH_2-$ or $-CH_2CH_2-$ group and R^{P2} and R^{P4} are each hydrogen; or

R^{P2} and R^{P4} are taken together to form a $-CH_2-$ or $-CH_2CH_2-$ group and R^{P1} and R^{P3} are each hydrogen.

28. The compound of any one of claims 1 to 25, wherein X^2 is:

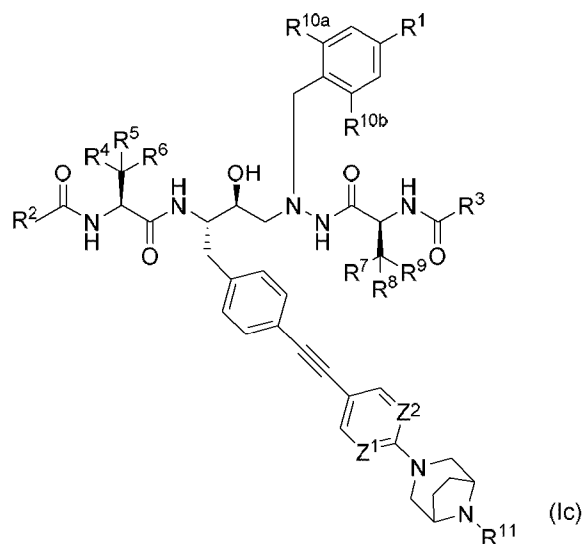


29. The compound of any one of claims 1 to 28, wherein X^2 is:



30. The compound of any one of claims 1 to 29, wherein R^{11} is 4 to 10-membered heterocyclyl having 1 to 3 heteroatoms selected from N, O, and S.

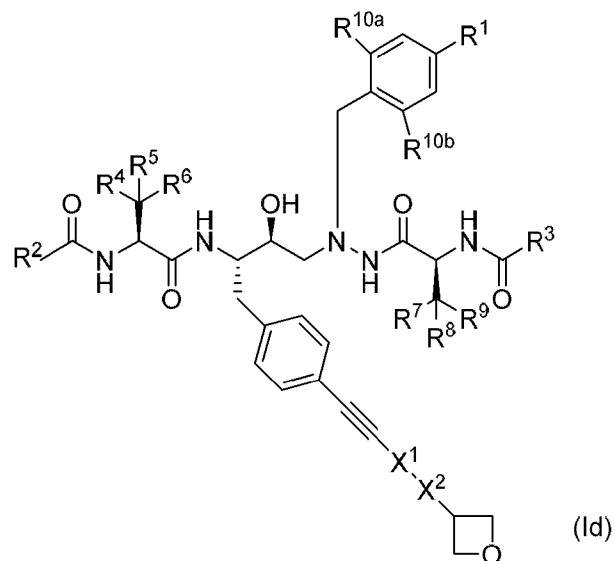
31. The compound of any one of claims 1 to 30, wherein R^{11} is a 4 to 6-membered heterocycle having one oxygen.
32. The compound of any one of claims 1 to 31, wherein R^{11} is oxetan-3-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl.
33. The compound of claim 1 or 2, wherein the compound of Formula (Ia) is a compound of Formula:



or a pharmaceutically acceptable salt thereof, wherein:

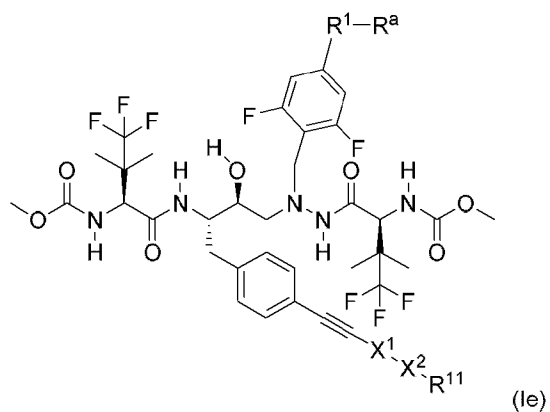
Z^1 and Z^2 are independently N or CH.

34. The compound of claim 1 or 2, wherein the compound of Formula (Ia) is a compound of Formula (Id):



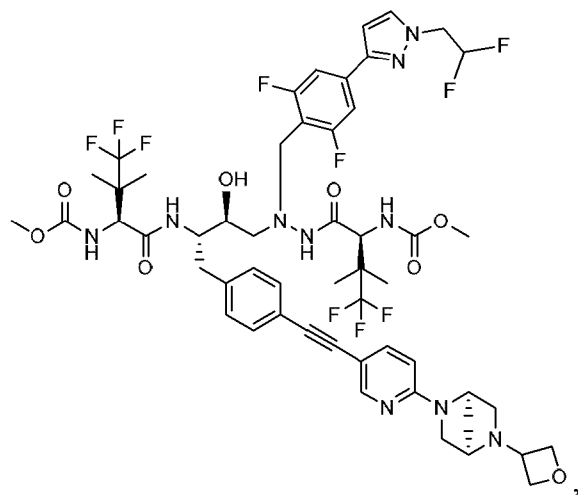
or a pharmaceutically acceptable salt thereof.

35. The compound of claim 1 or 2, wherein the compound of Formula (Ia) is a compound of Formula (Ie):

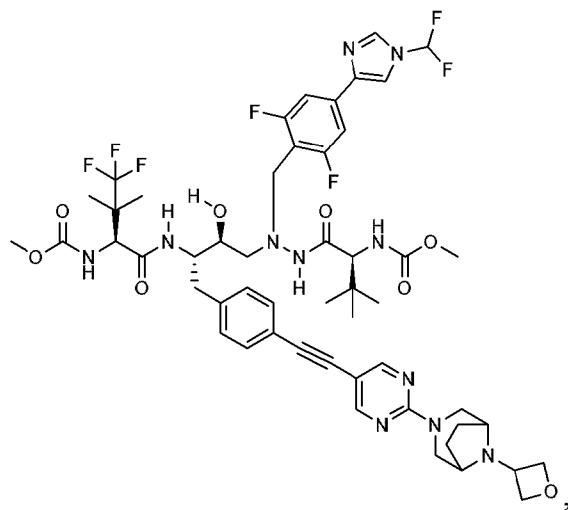


or a pharmaceutically acceptable salt thereof.

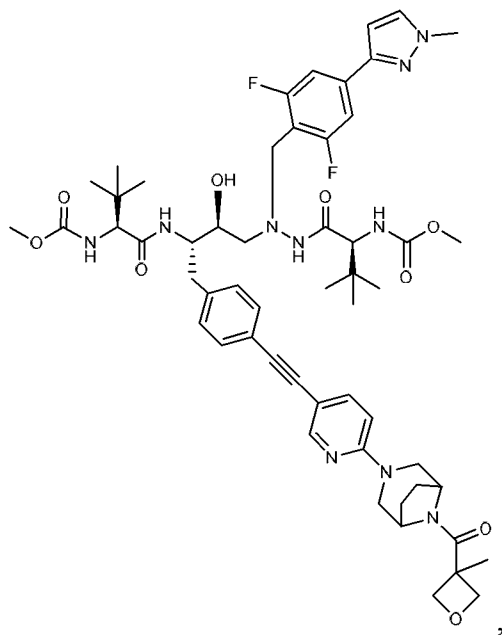
36. A compound, or a pharmaceutically acceptable salt thereof, selected from:



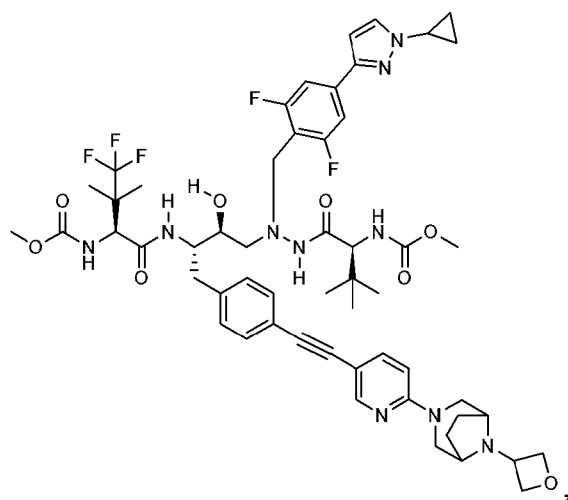
EXAMPLE 1



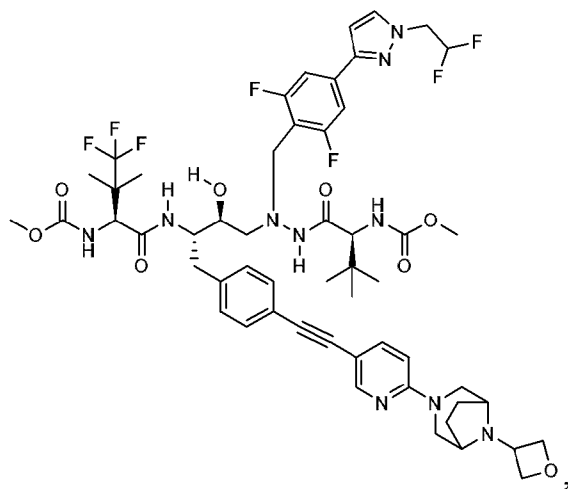
EXAMPLE 2



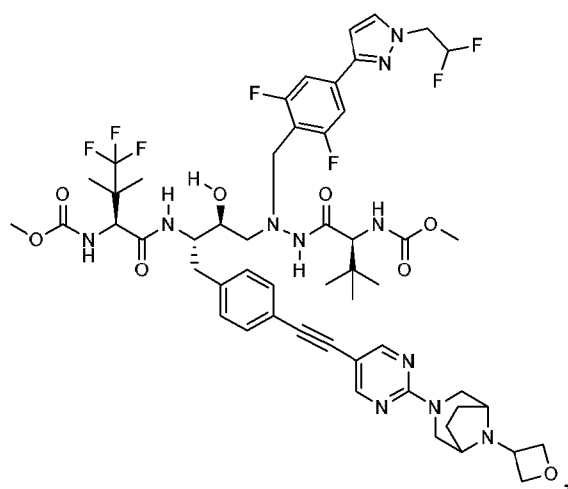
EXAMPLE 4



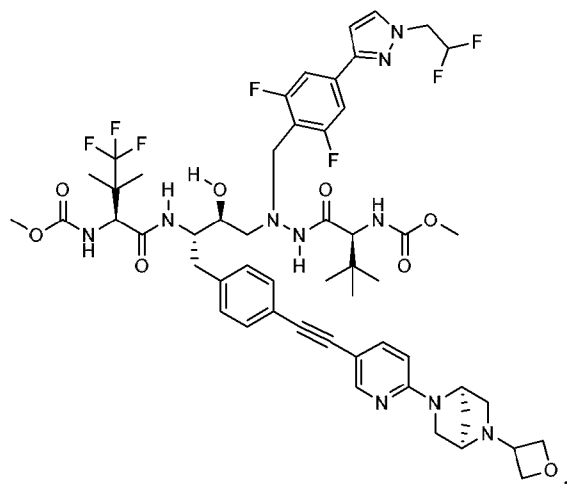
EXAMPLE 5



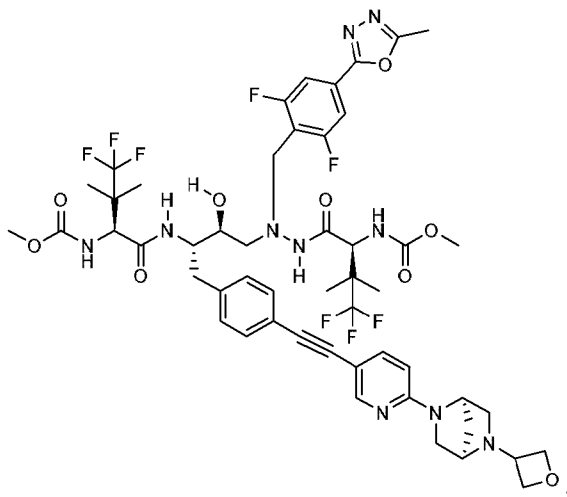
EXAMPLE 6



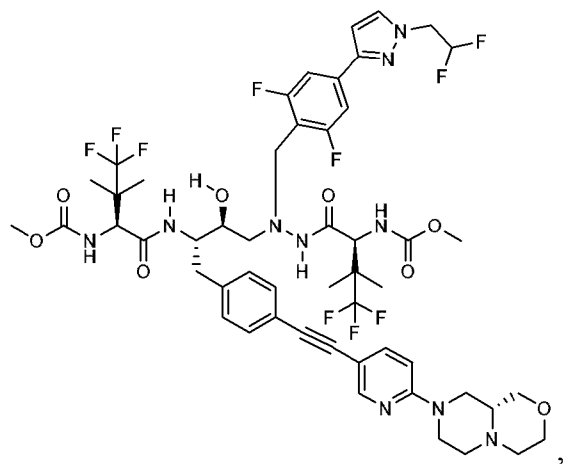
EXAMPLE 7



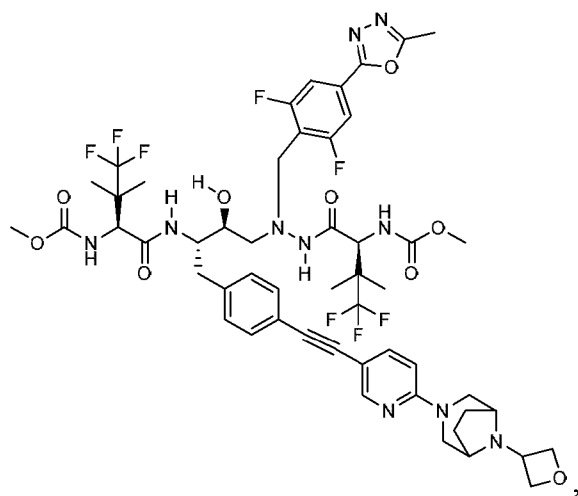
EXAMPLE 8



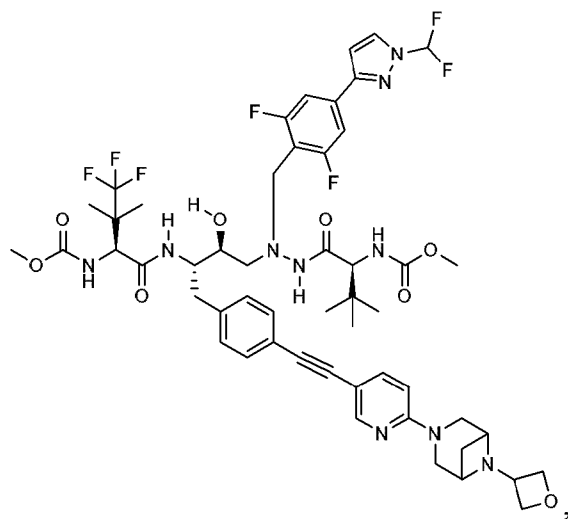
EXAMPLE 9



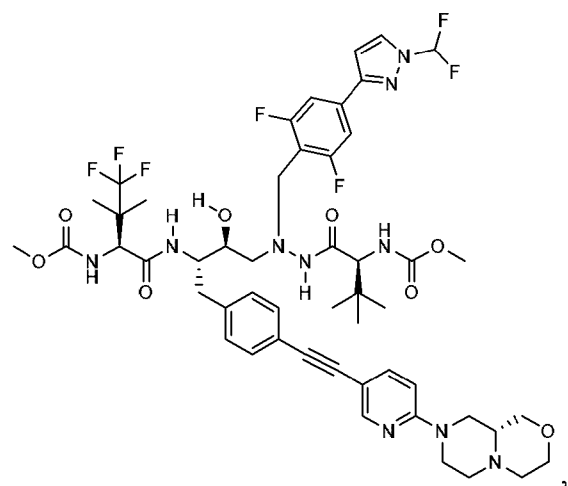
EXAMPLE 10



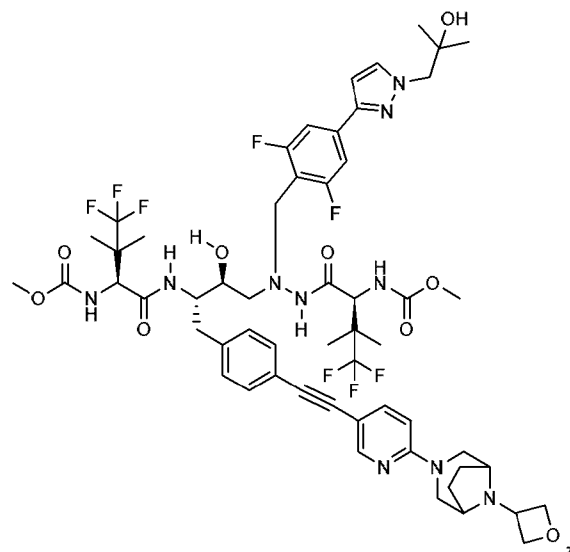
EXAMPLE 11



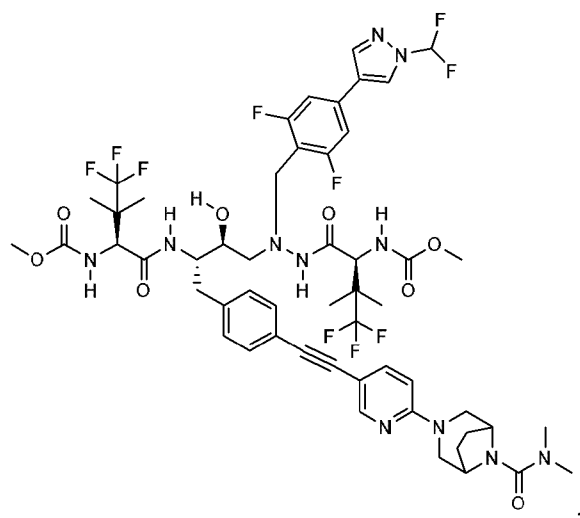
EXAMPLE 12



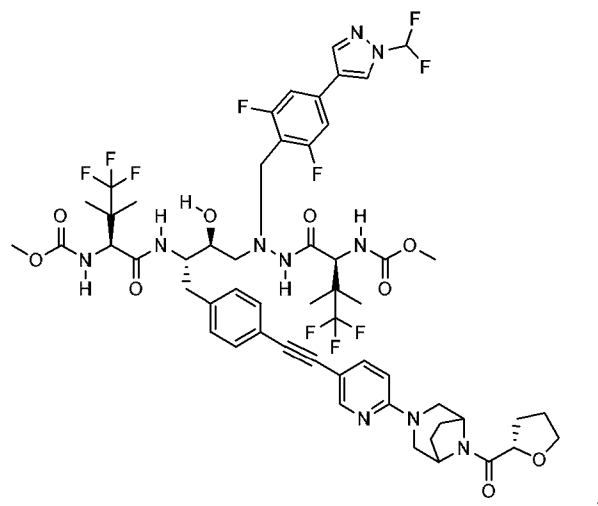
EXAMPLE 13



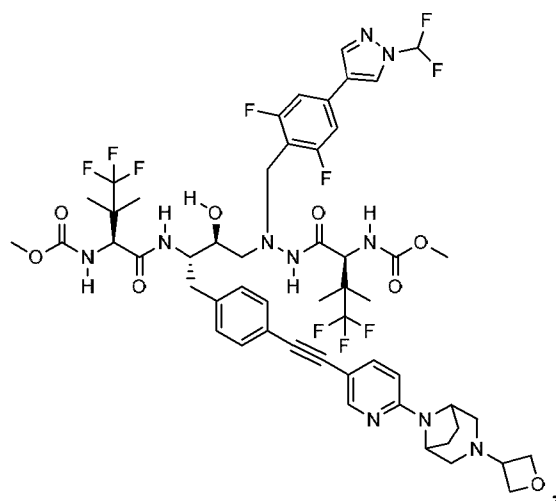
EXAMPLE 16



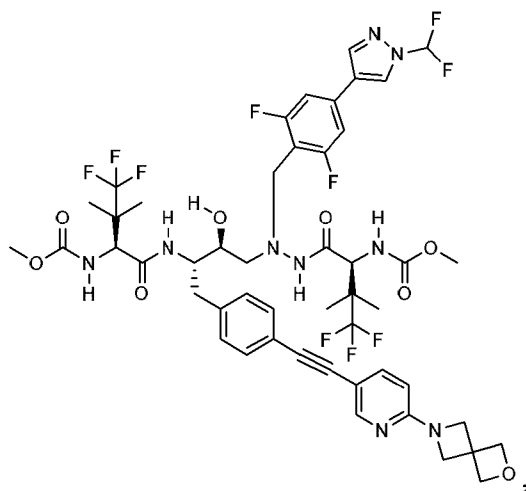
EXAMPLE 17



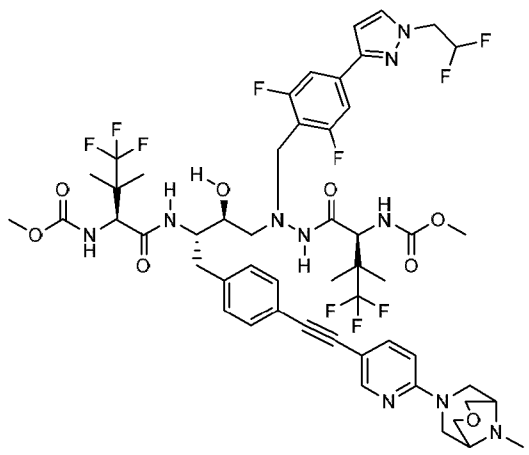
EXAMPLE 18



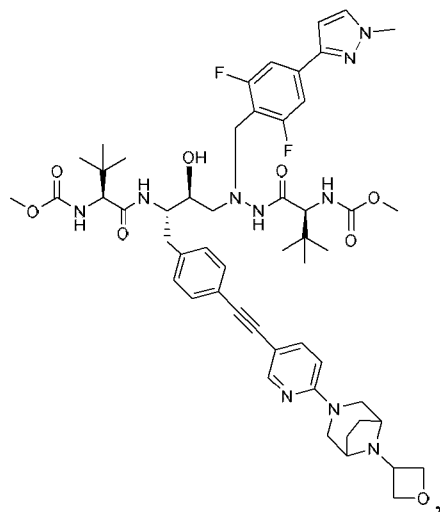
EXAMPLE 19



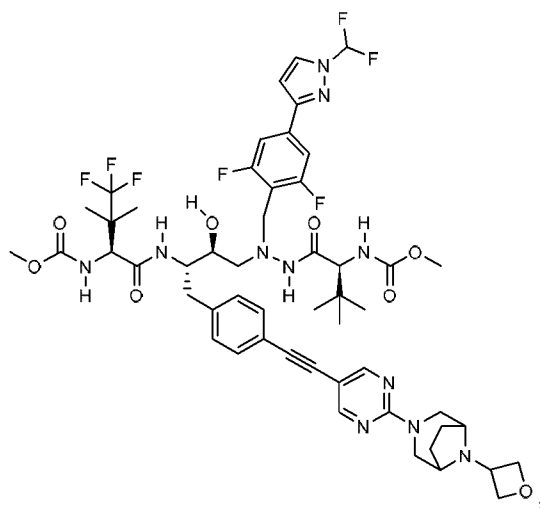
EXAMPLE 20



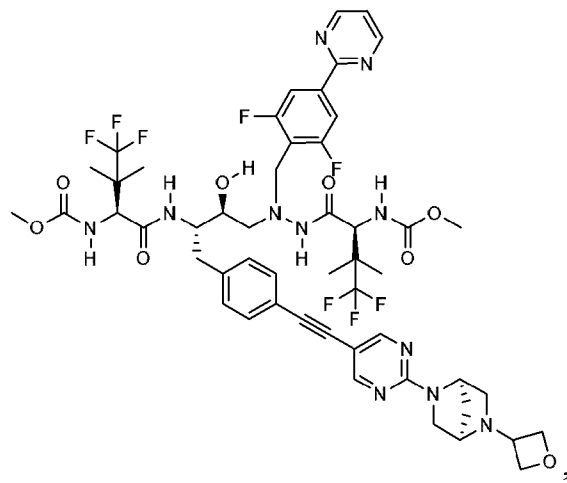
EXAMPLE 21



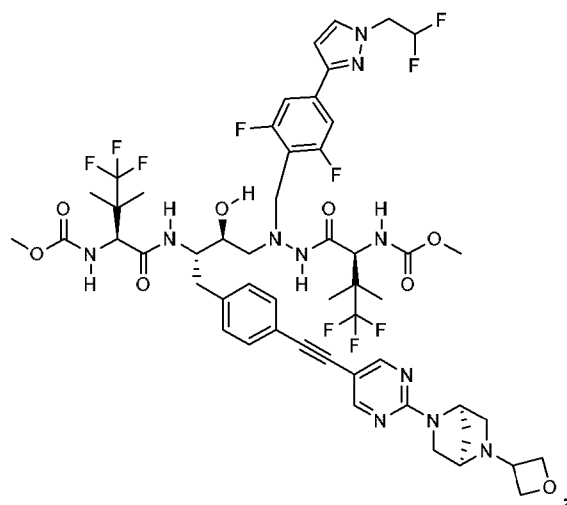
EXAMPLE 22



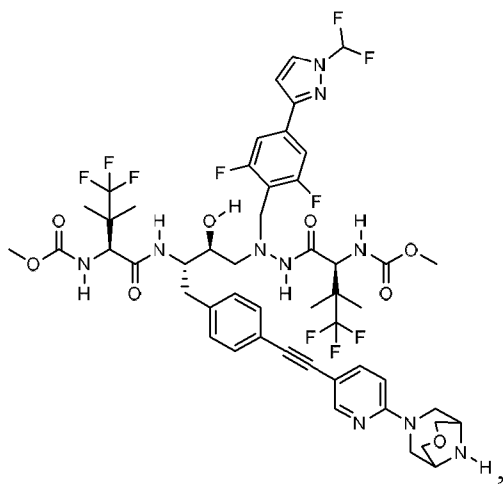
EXAMPLE 23



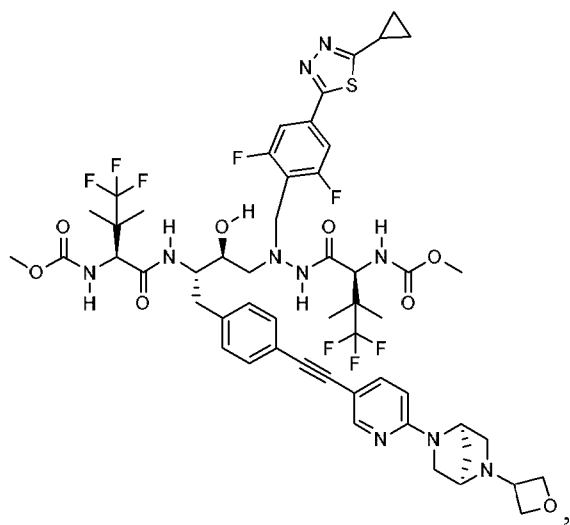
EXAMPLE 24



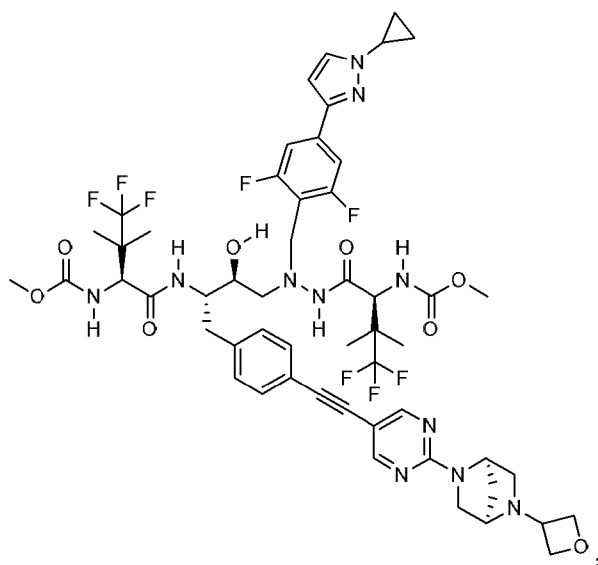
EXAMPLE 25



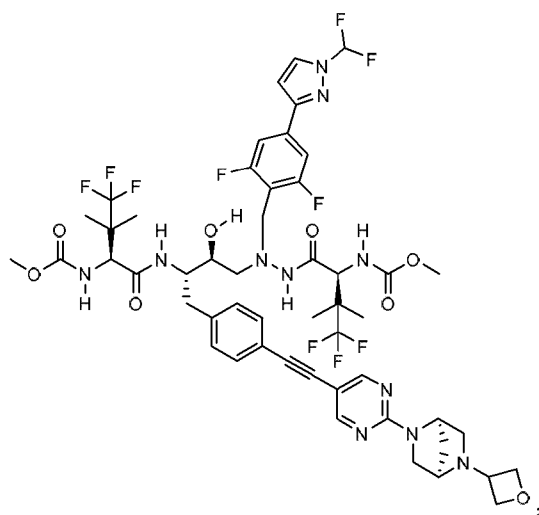
EXAMPLE 26



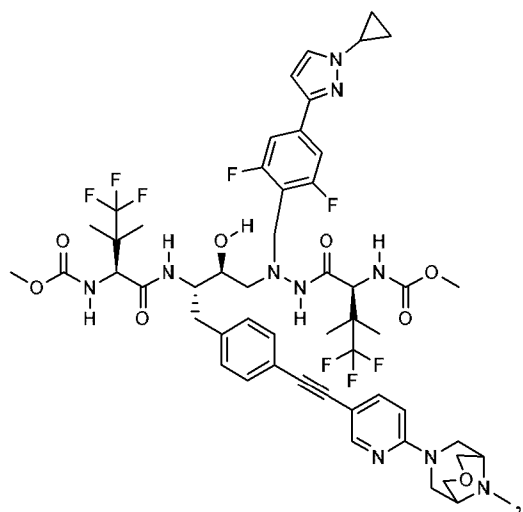
EXAMPLE 27



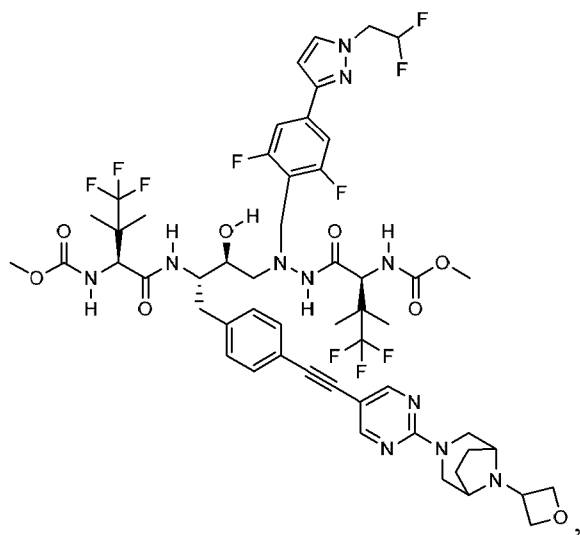
EXAMPLE 31



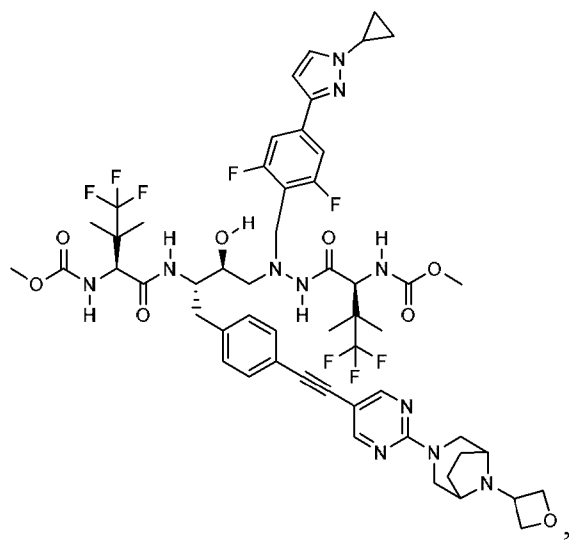
EXAMPLE 32



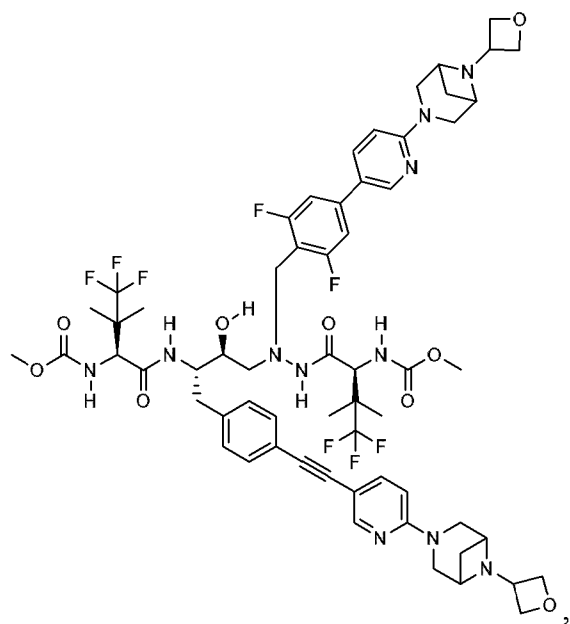
EXAMPLE 35



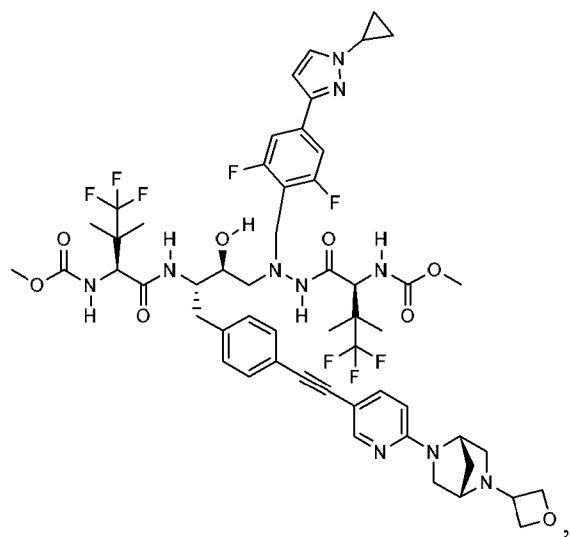
EXAMPLE 36



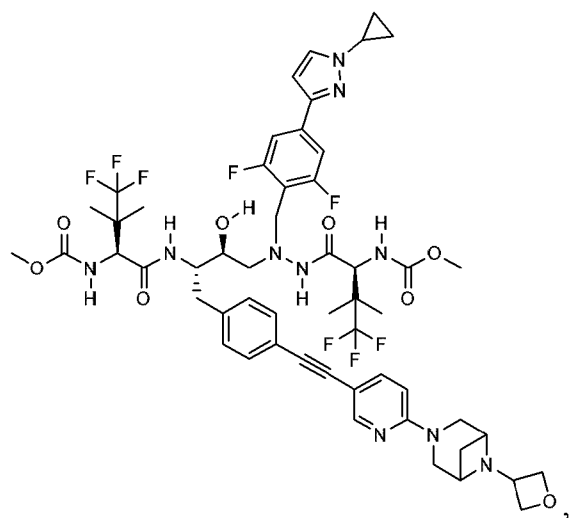
EXAMPLE 37



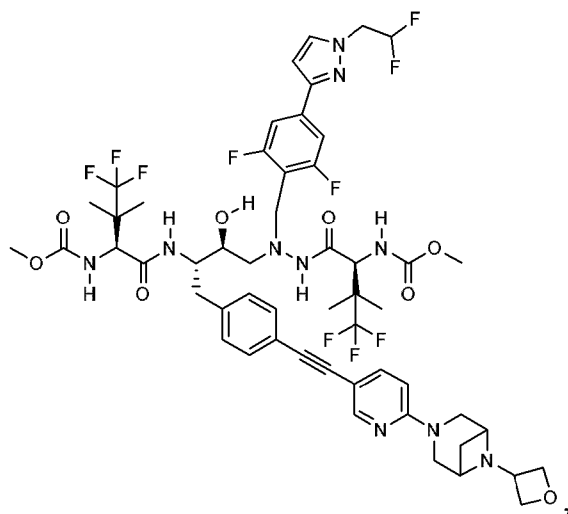
EXAMPLE 38



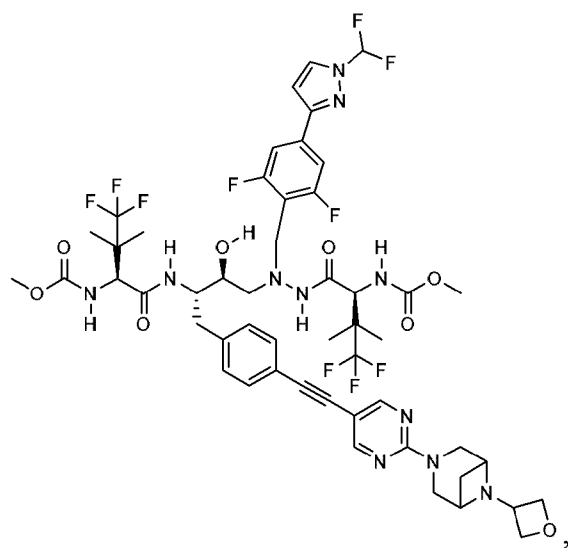
EXAMPLE 39



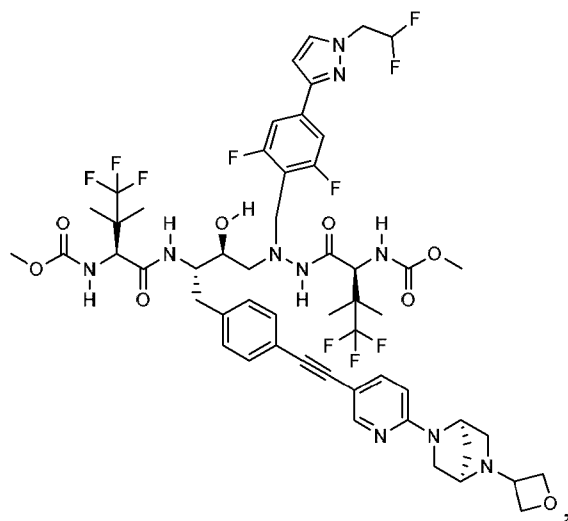
EXAMPLE 40



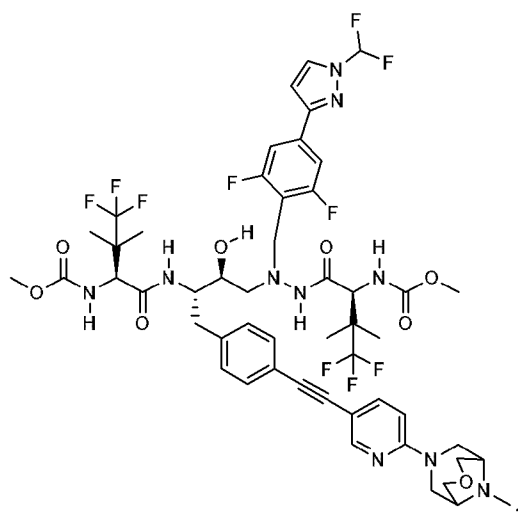
EXAMPLE 41



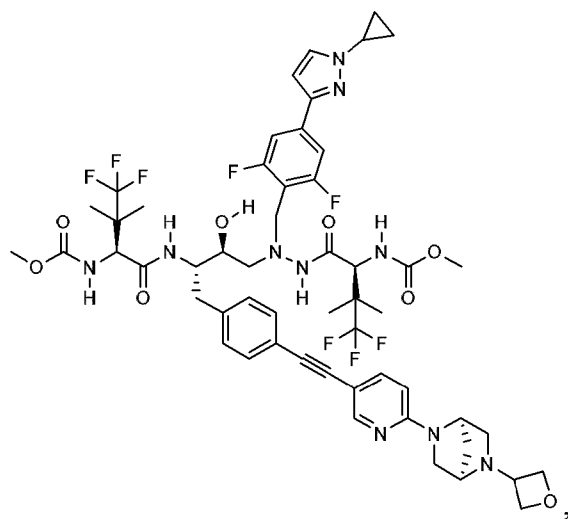
EXAMPLE 42



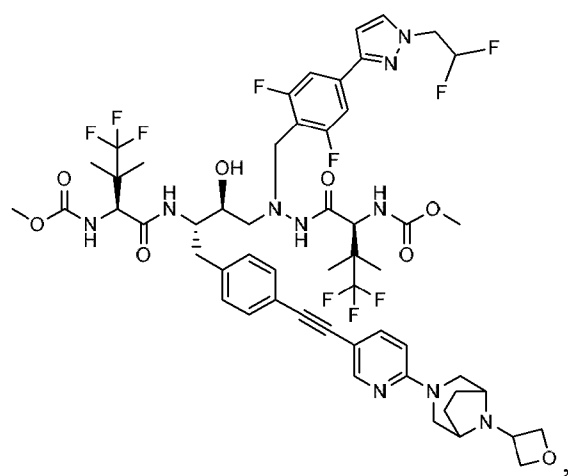
EXAMPLE 43



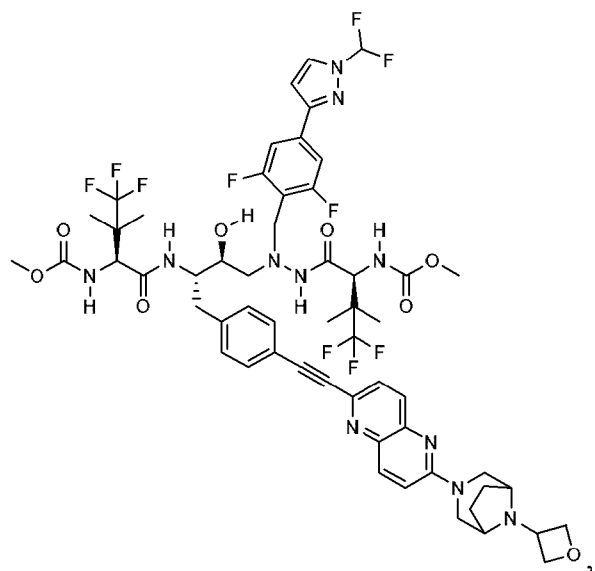
EXAMPLE 44



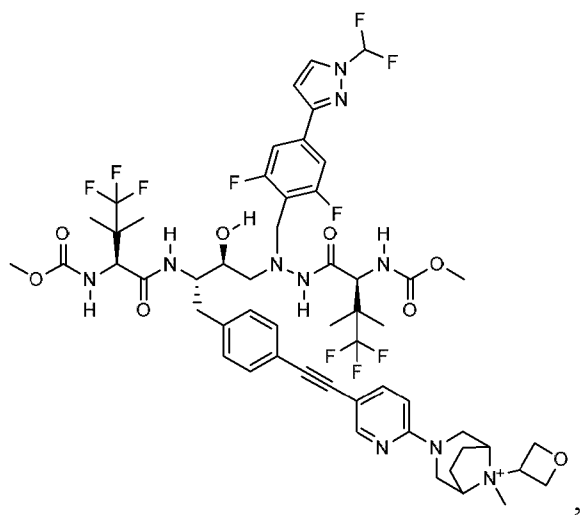
EXAMPLE 45



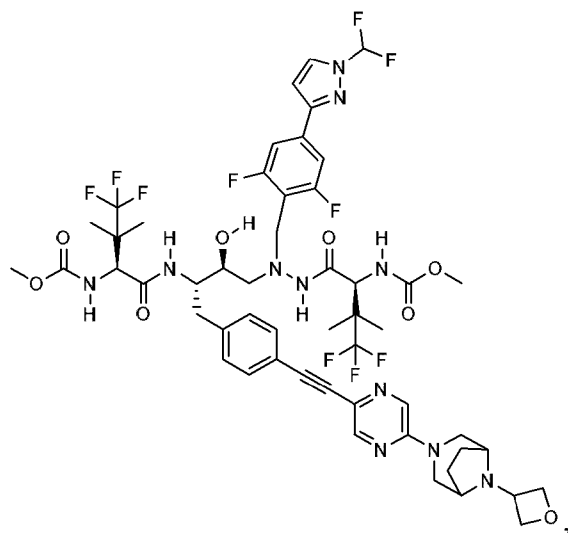
EXAMPLE 46



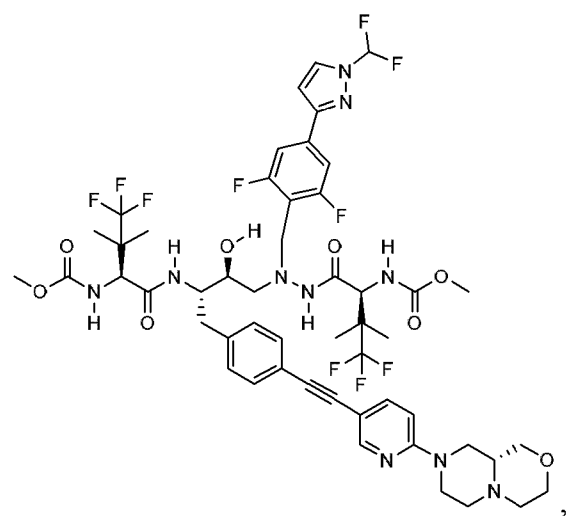
EXAMPLE 47



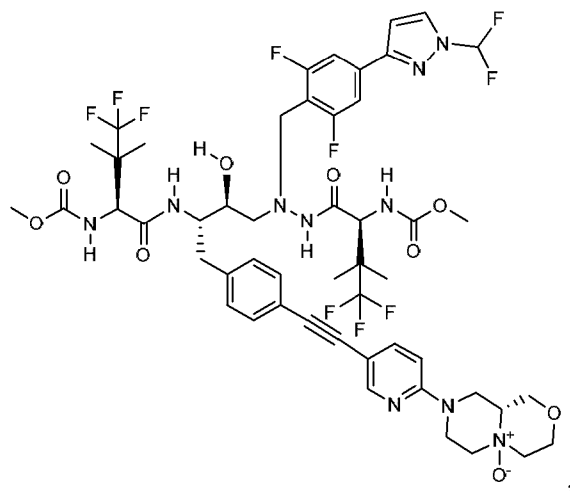
EXAMPLE 48



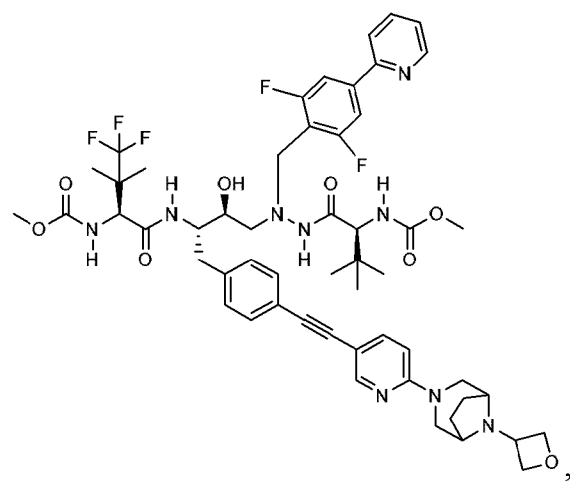
EXAMPLE 50



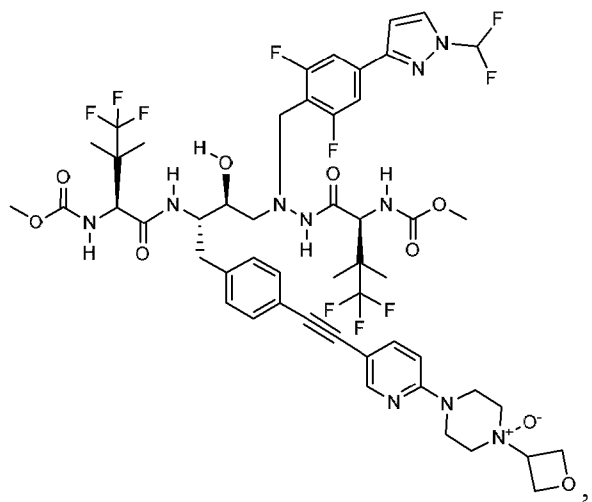
EXAMPLE 51



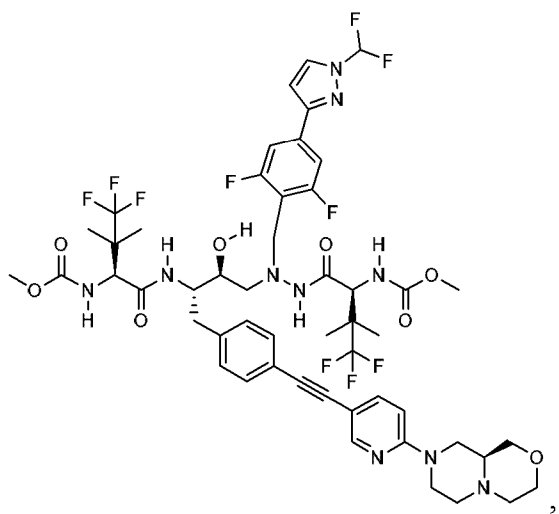
EXAMPLE 52



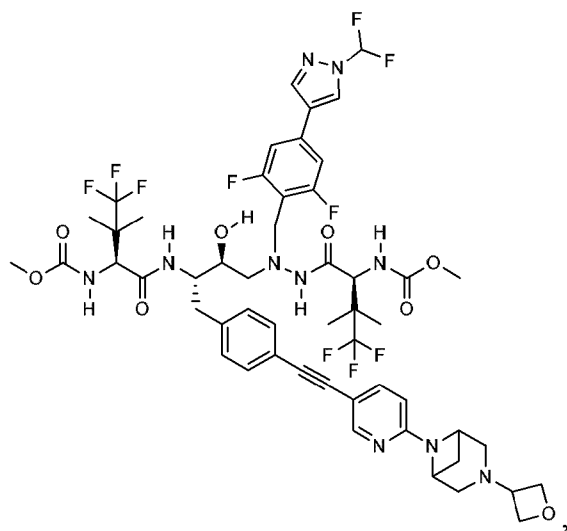
EXAMPLE 53



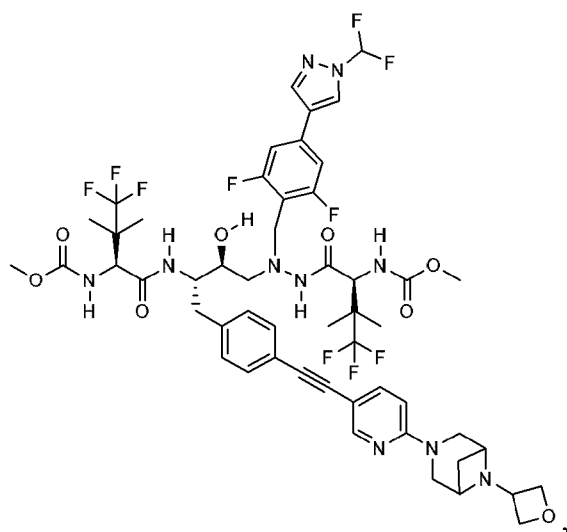
EXAMPLE 54



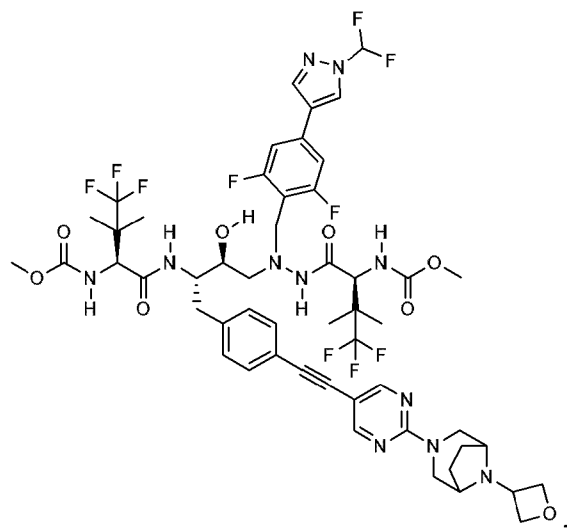
EXAMPLE 55



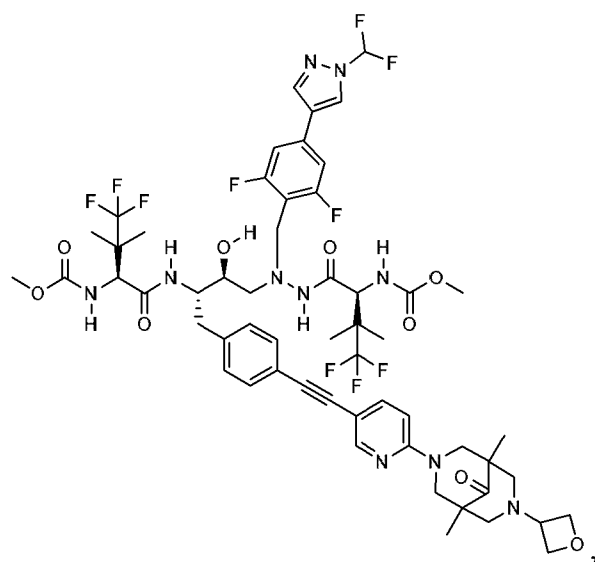
EXAMPLE 59



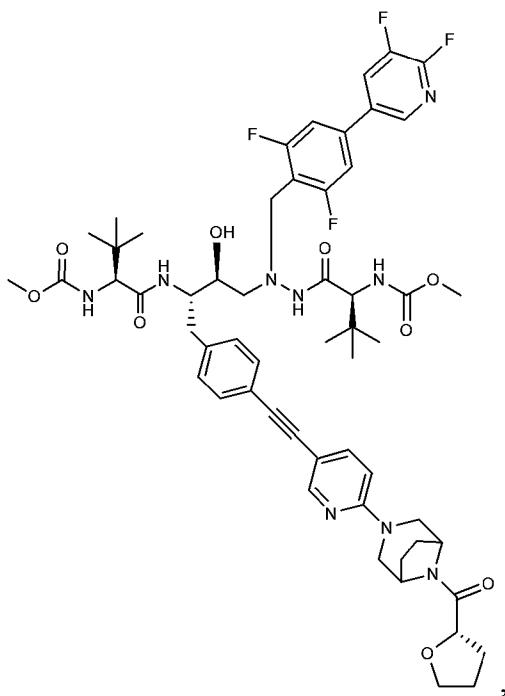
EXAMPLE 60



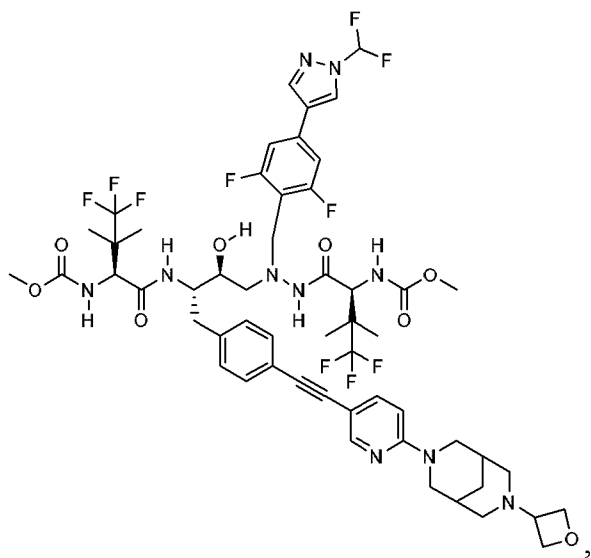
EXAMPLE 61



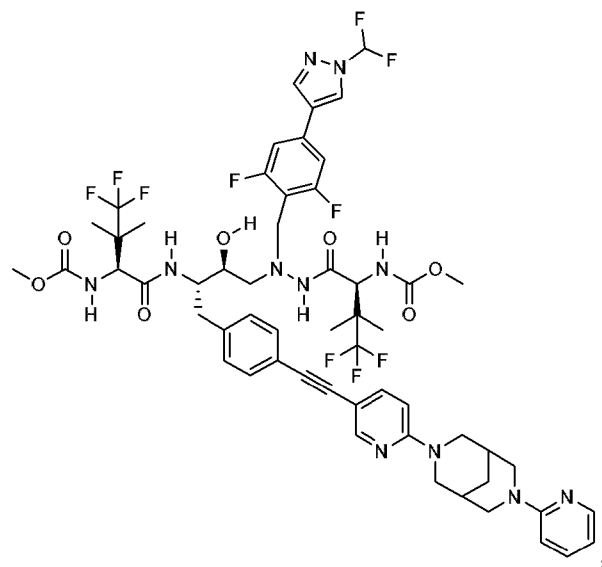
EXAMPLE 62



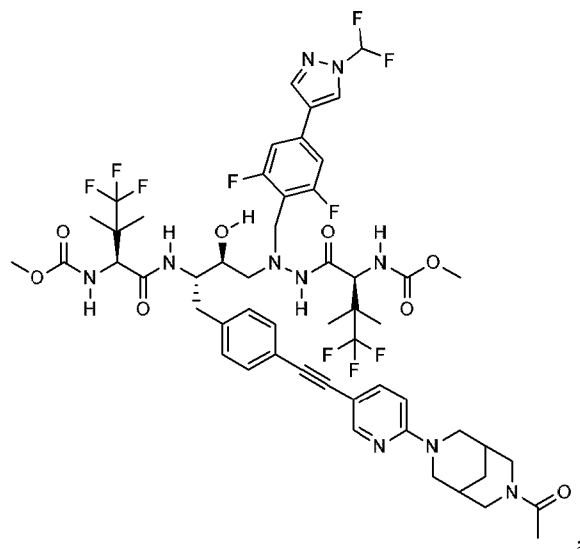
EXAMPLE 64



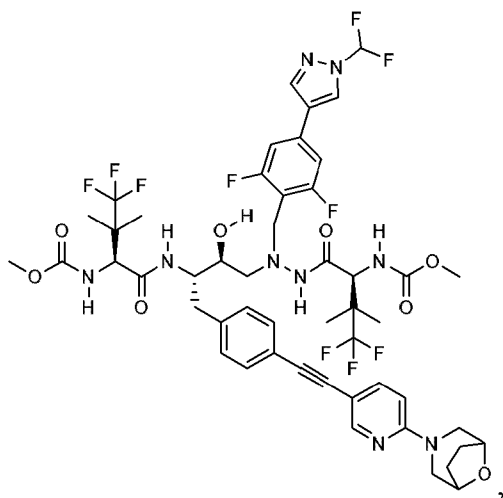
EXAMPLE 65



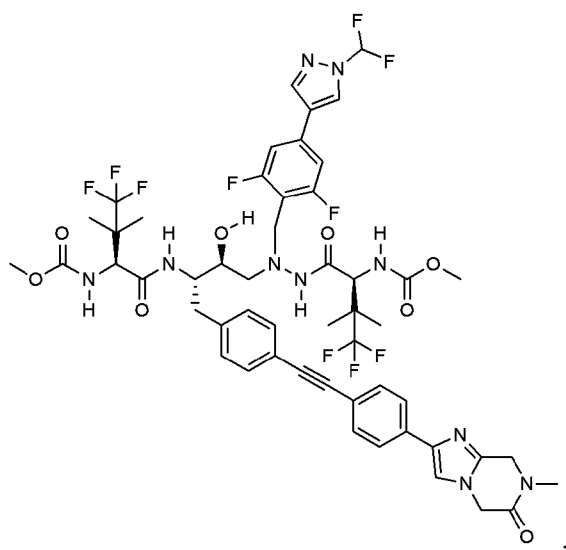
EXAMPLE 66



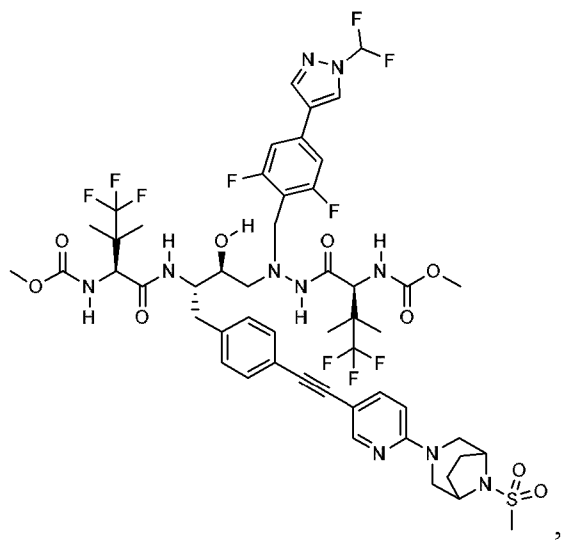
EXAMPLE 67



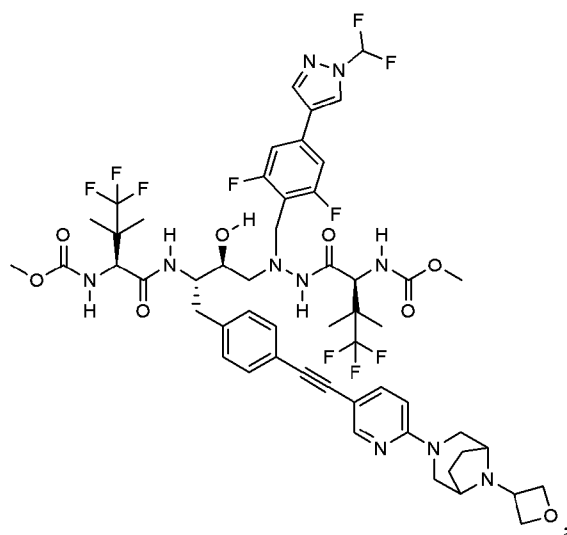
EXAMPLE 68



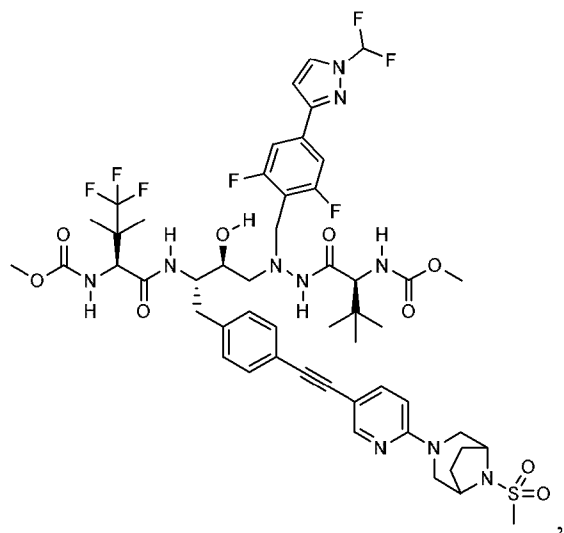
EXAMPLE 69



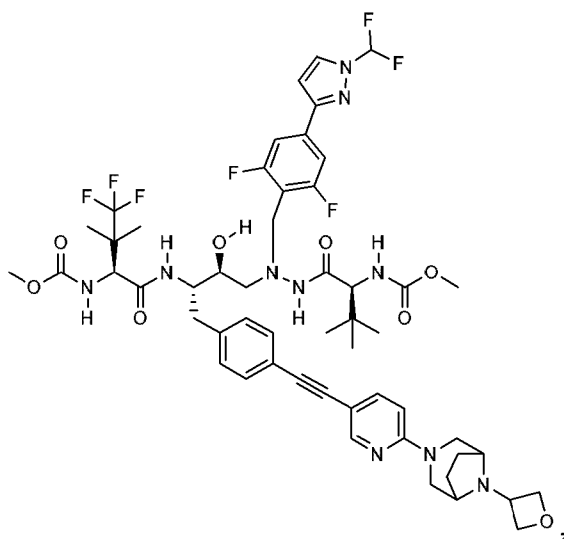
EXAMPLE 70



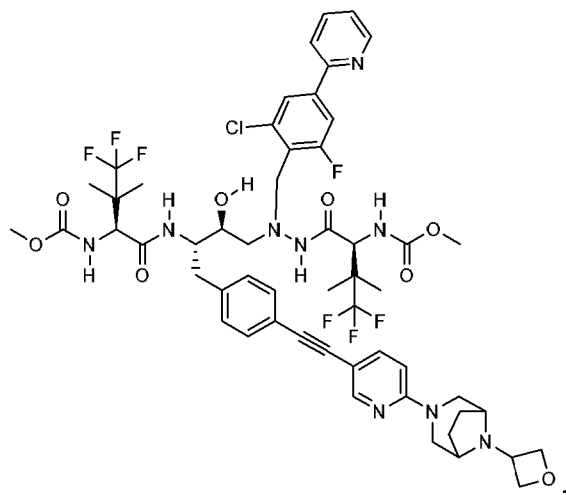
EXAMPLE 71



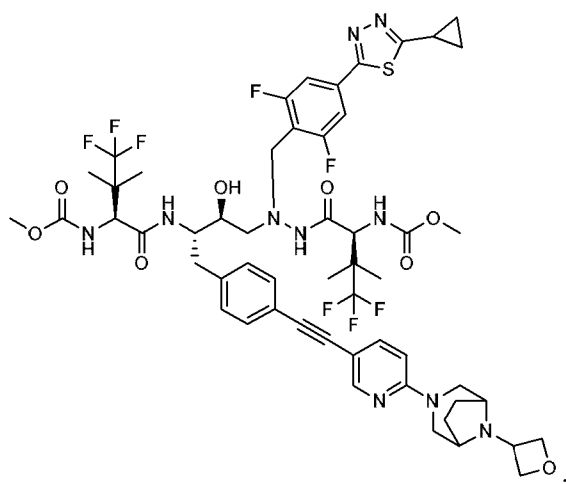
EXAMPLE 72



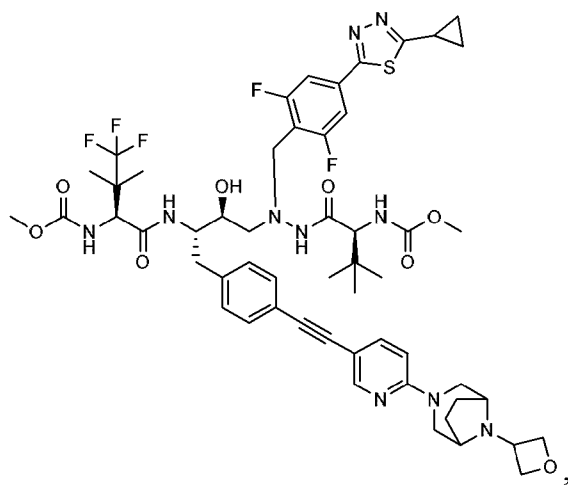
EXAMPLE 73



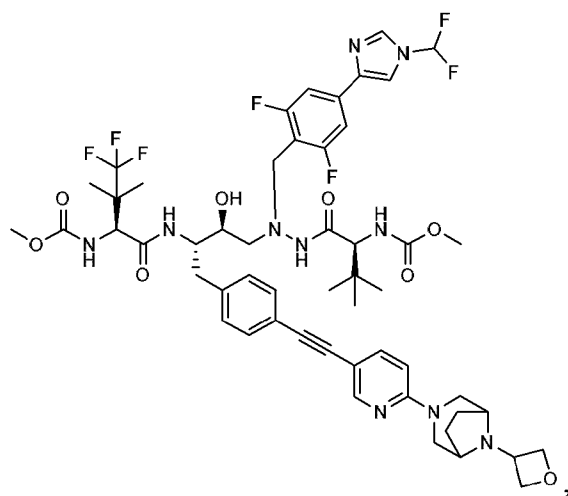
EXAMPLE 74



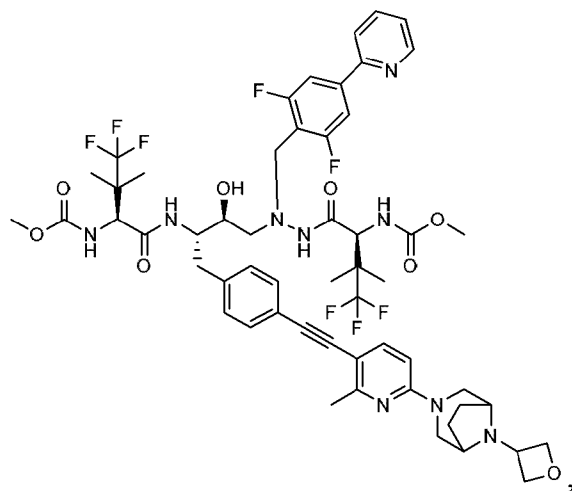
EXAMPLE 75



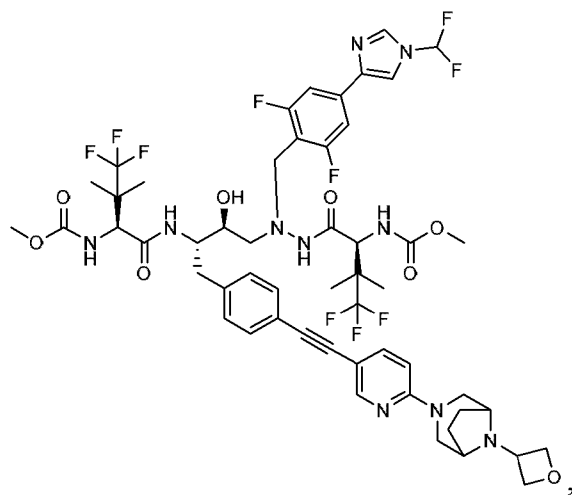
EXAMPLE 76



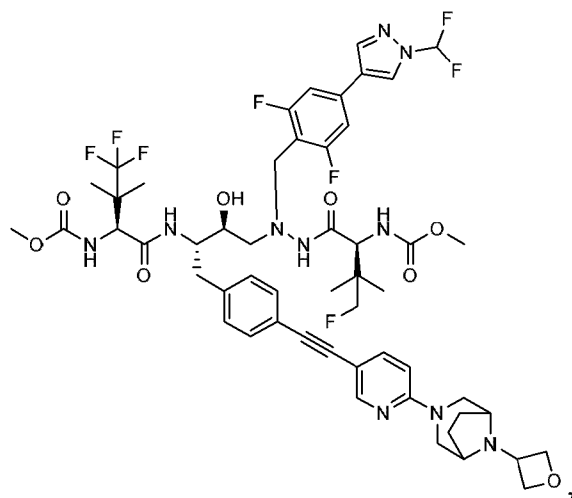
EXAMPLE 77



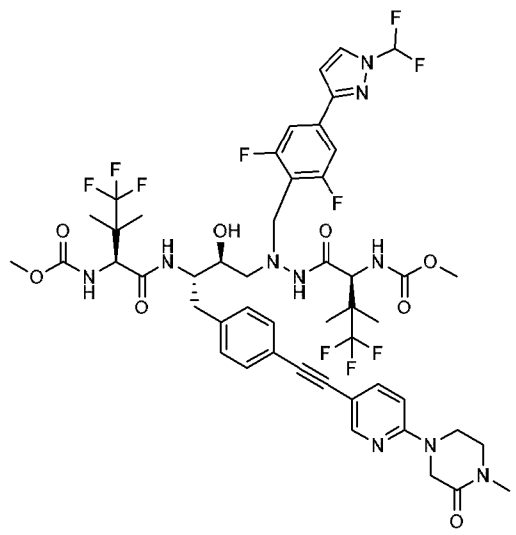
EXAMPLE 78



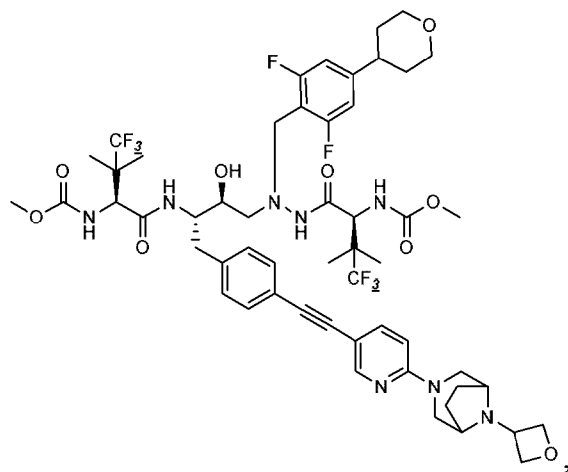
EXAMPLE 79



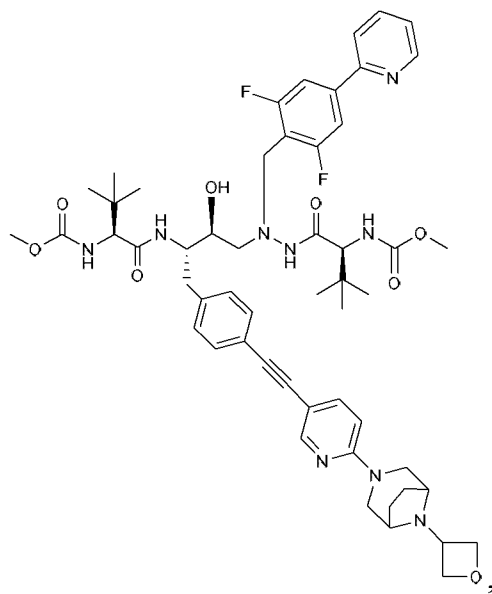
EXAMPLE 80



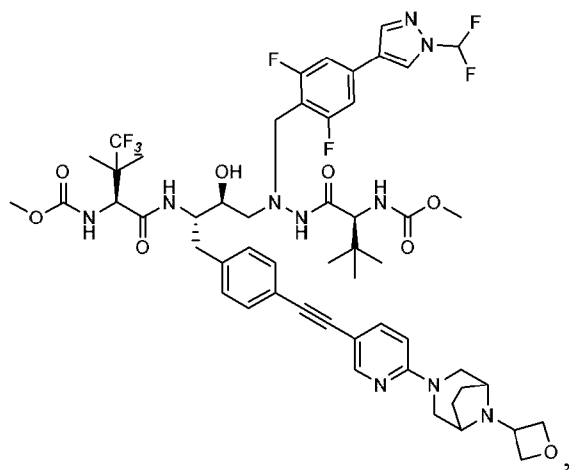
EXAMPLE 81



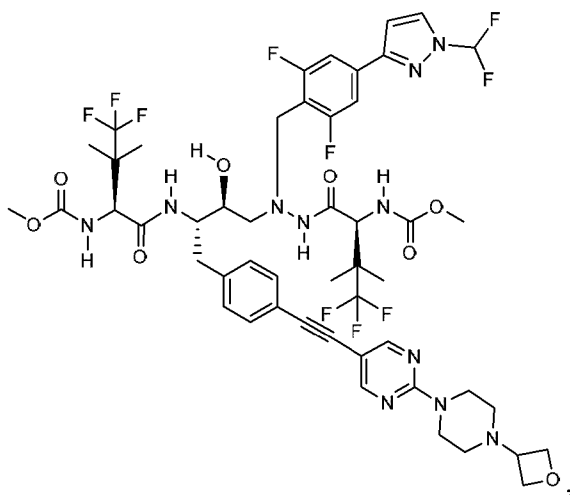
EXAMPLE 82



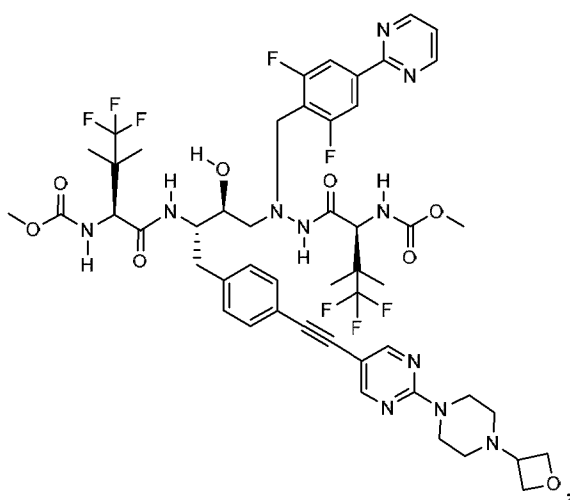
EXAMPLE 84



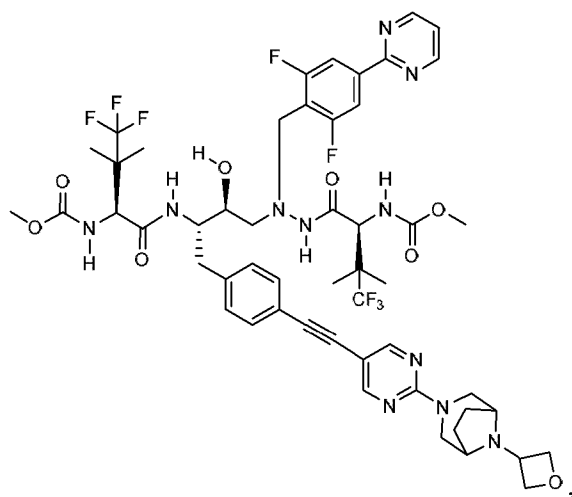
EXAMPLE 86



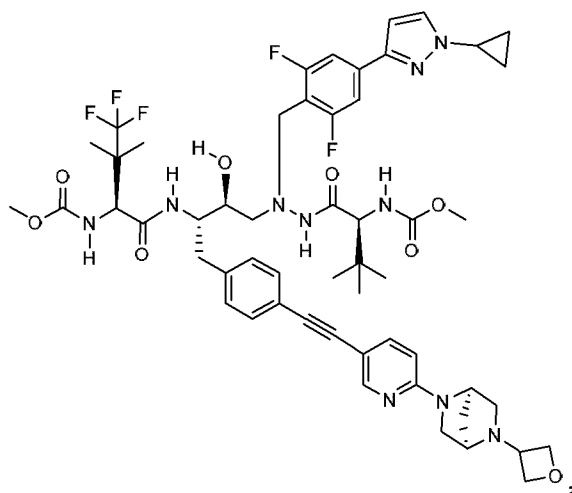
EXAMPLE 87



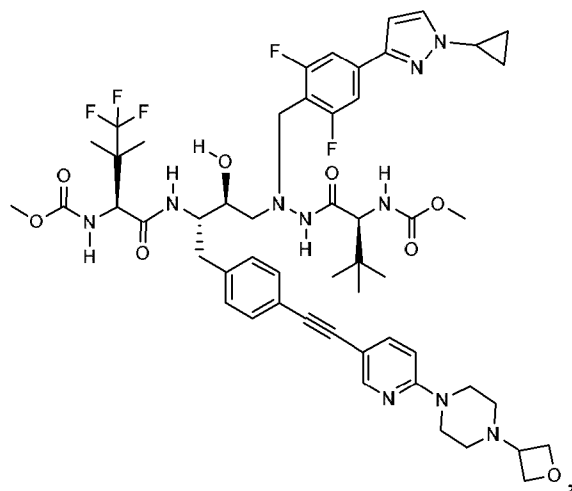
EXAMPLE 88



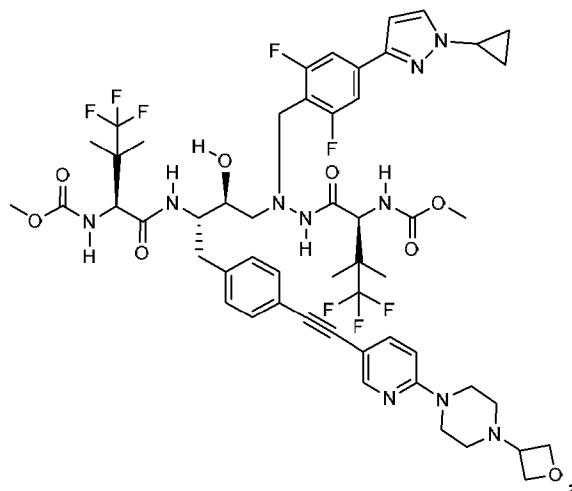
EXAMPLE 89



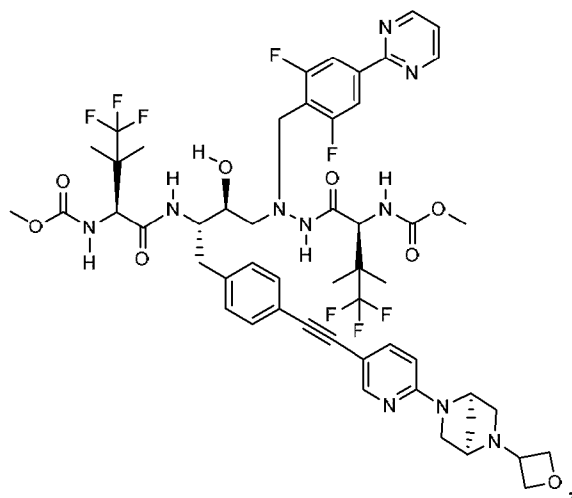
EXAMPLE 90



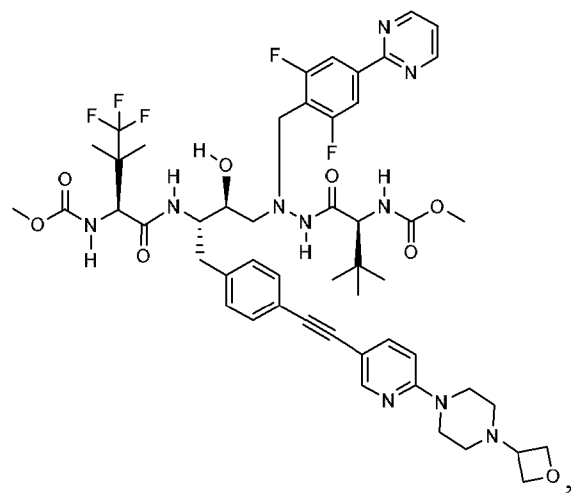
EXAMPLE 91



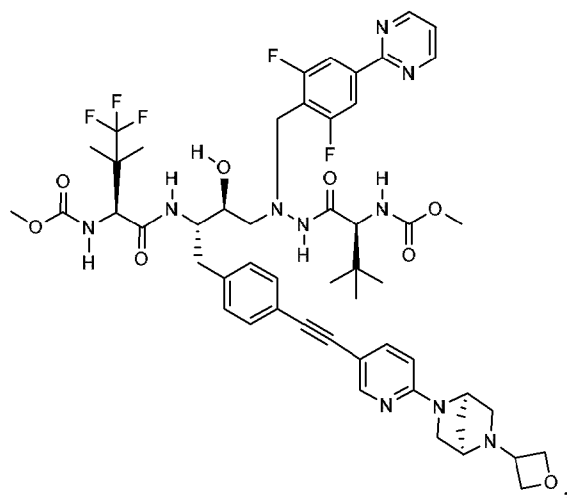
EXAMPLE 92



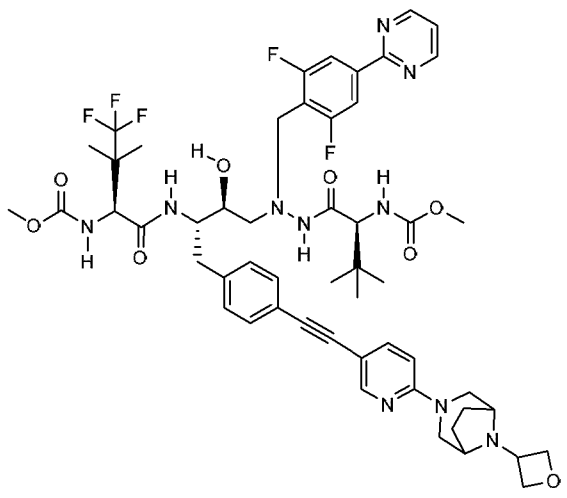
EXAMPLE 93



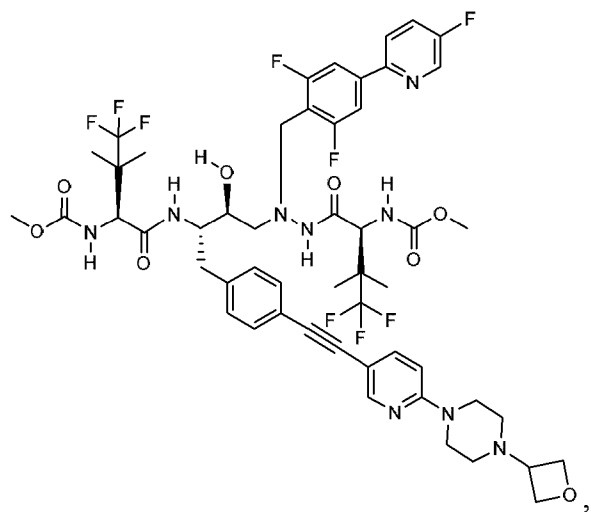
EXAMPLE 94



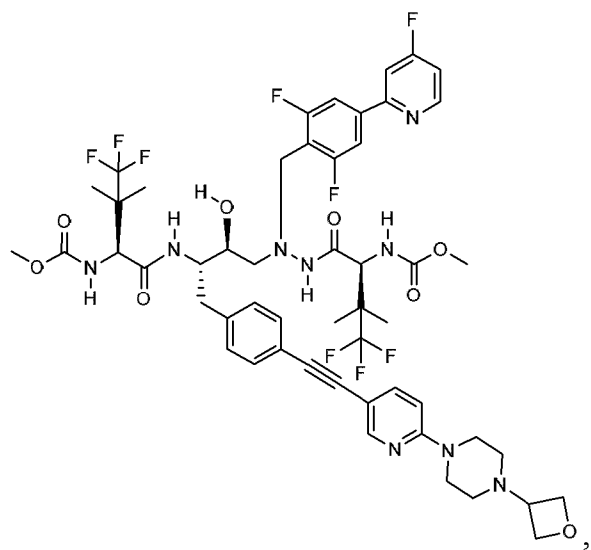
EXAMPLE 95



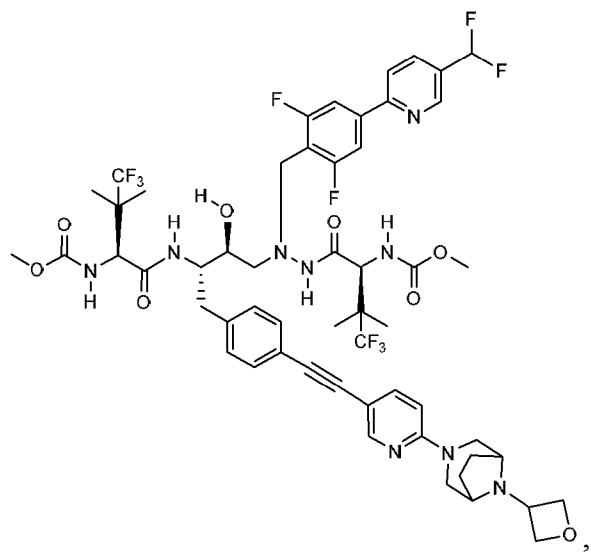
EXAMPLE 96



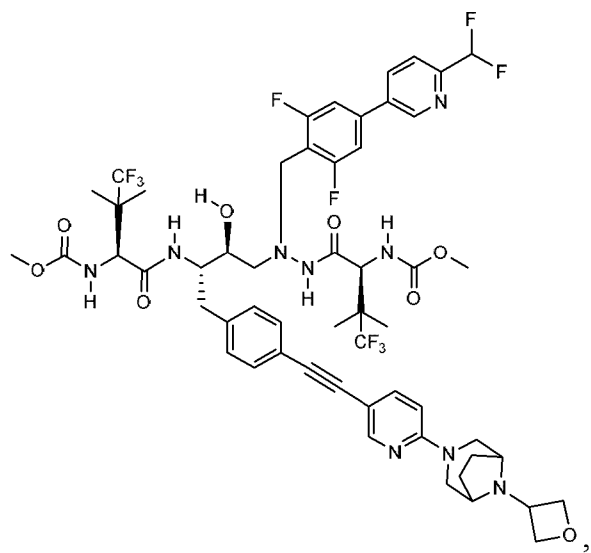
EXAMPLE 97



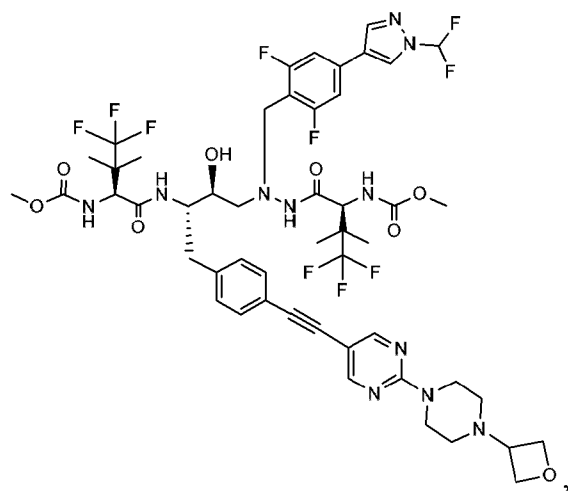
EXAMPLE 98



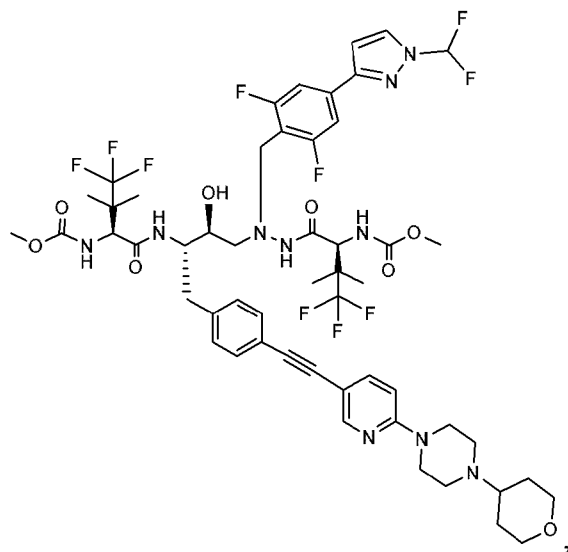
EXAMPLE 99



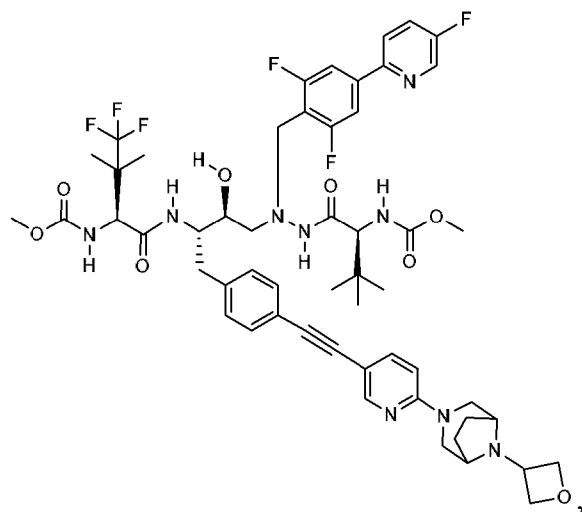
EXAMPLE 100



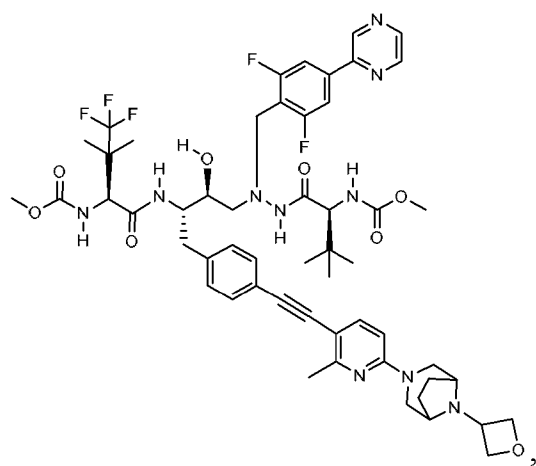
EXAMPLE 103



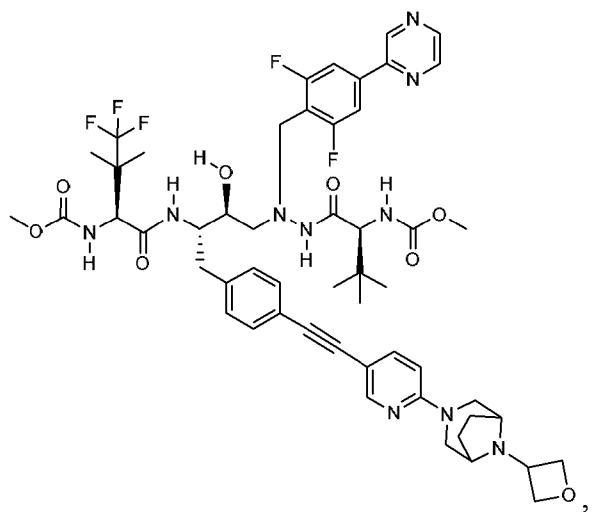
EXAMPLE 104



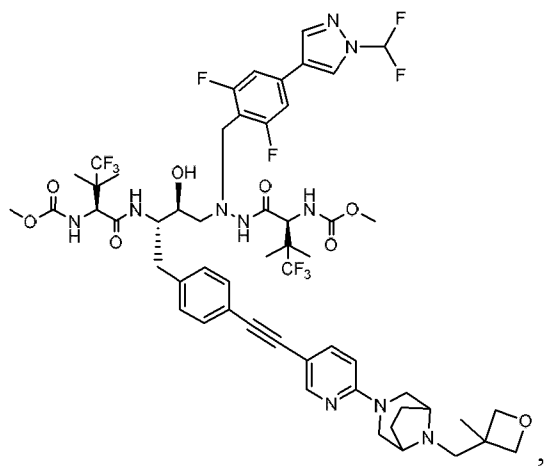
EXAMPLE 105



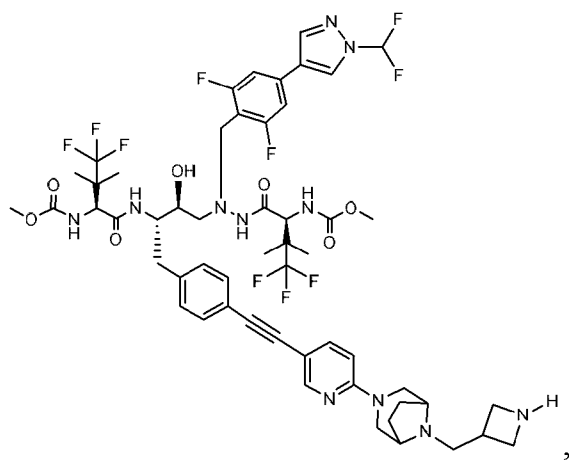
EXAMPLE 106



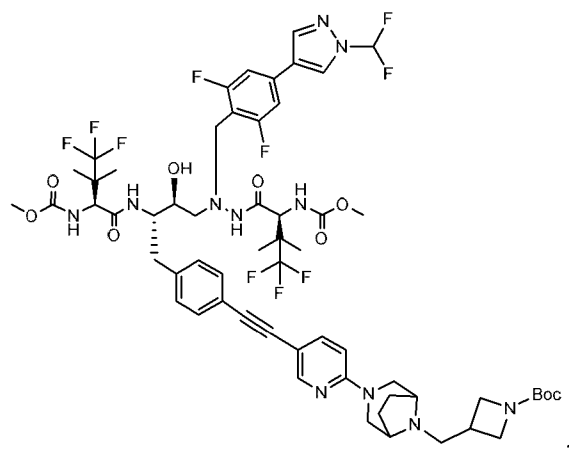
EXAMPLE 107



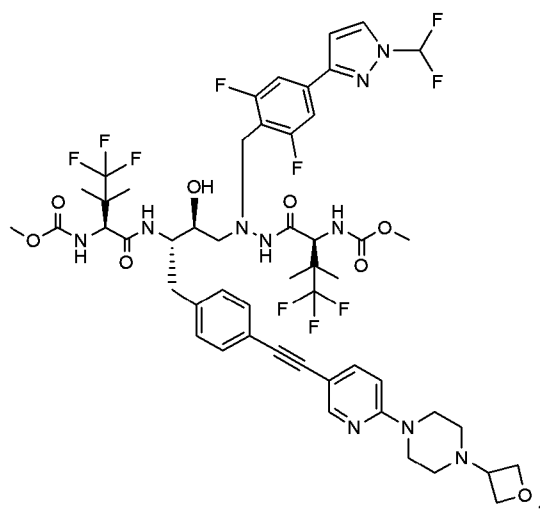
EXAMPLE 108



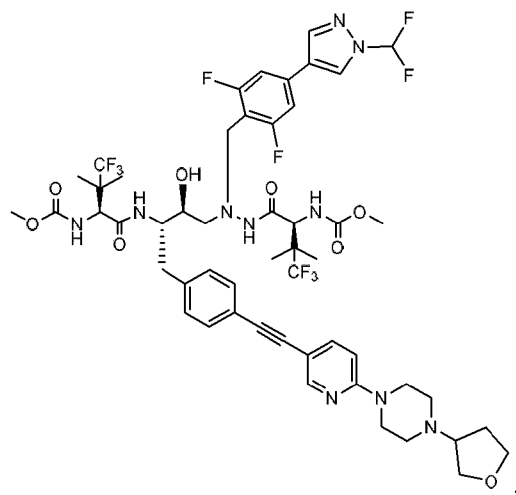
EXAMPLE 109



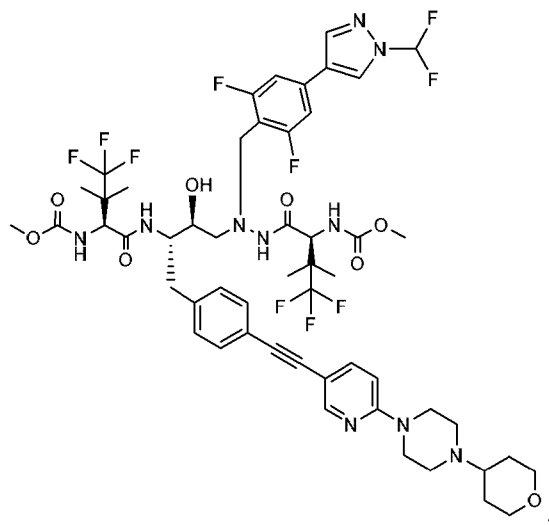
EXAMPLE 110



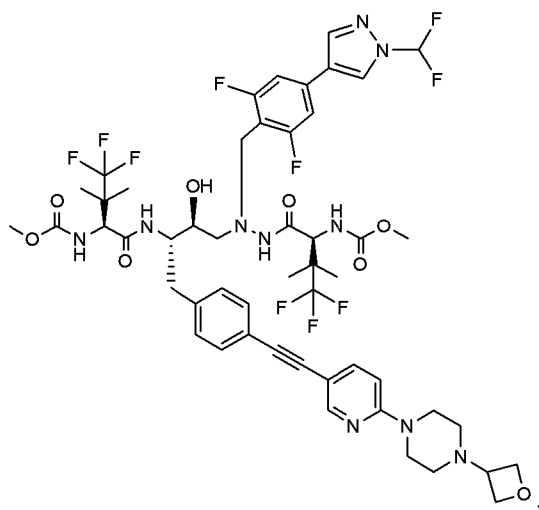
EXAMPLE 112



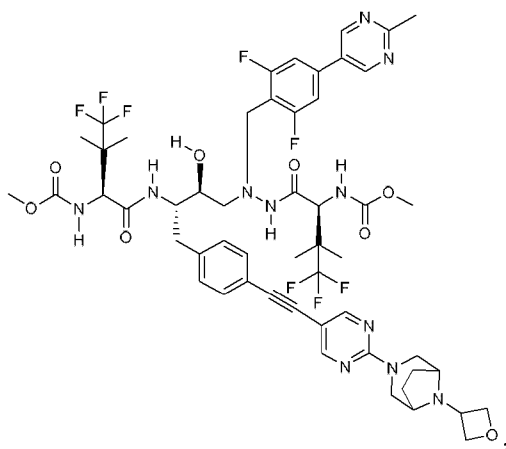
EXAMPLE 114



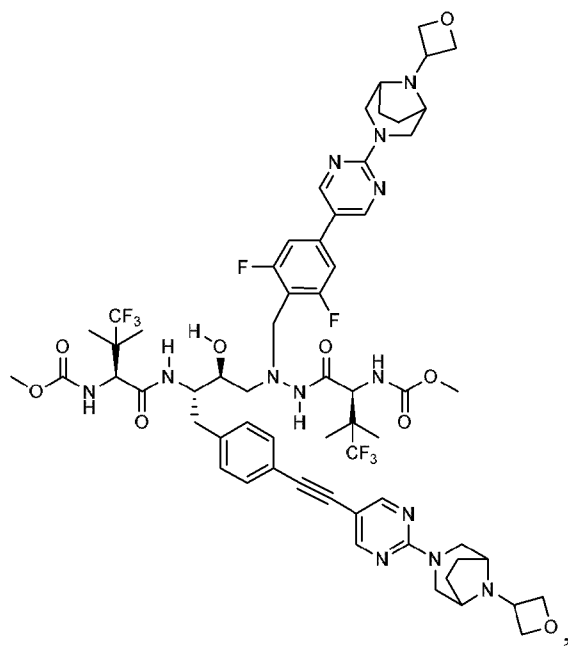
EXAMPLE 115



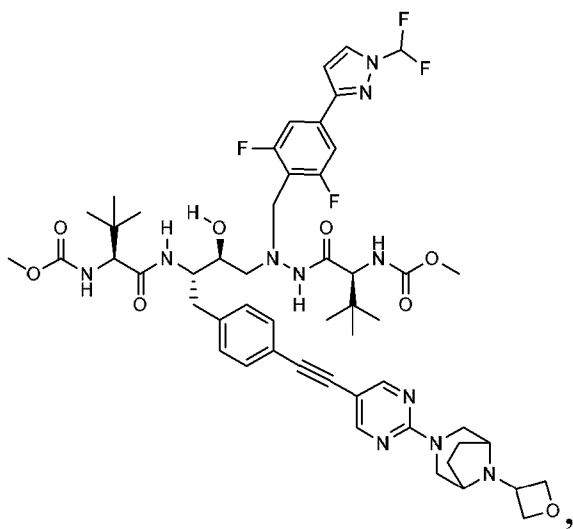
EXAMPLE 116



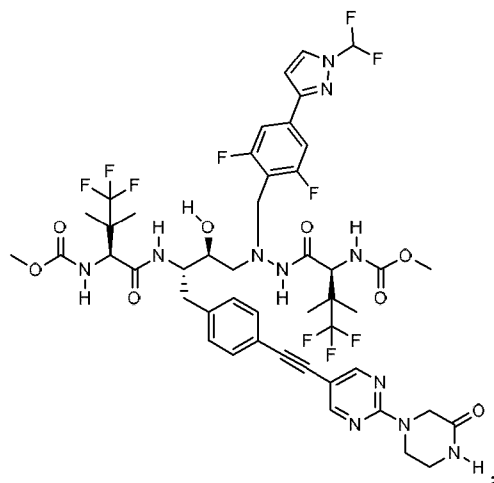
EXAMPLE 119



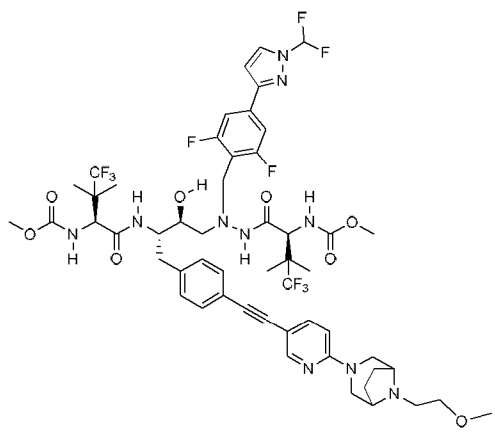
EXAMPLE 120



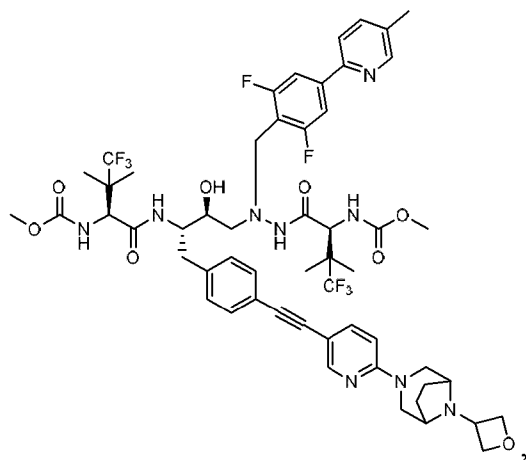
EXAMPLE 121



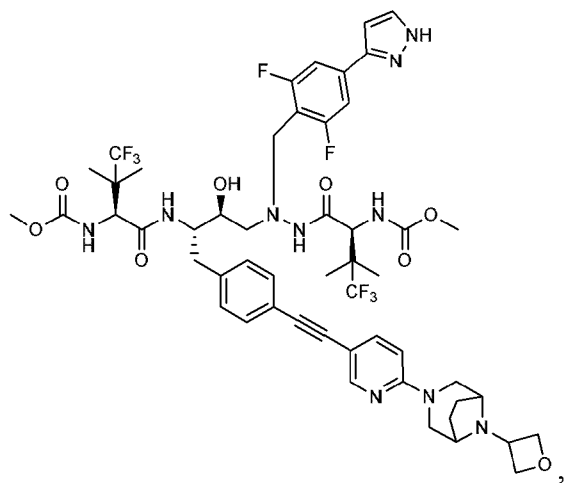
EXAMPLE 123



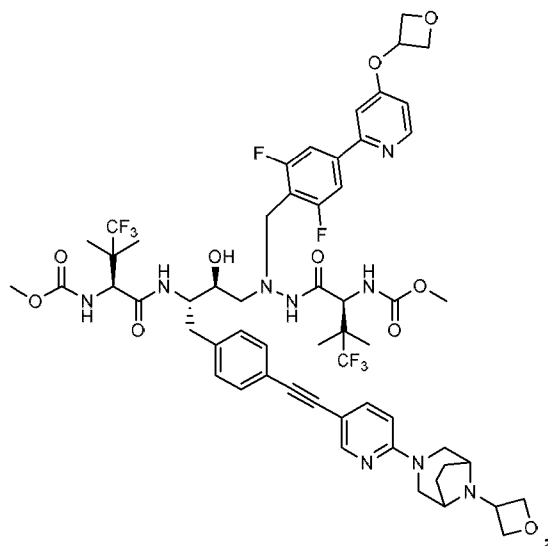
EXAMPLE 124



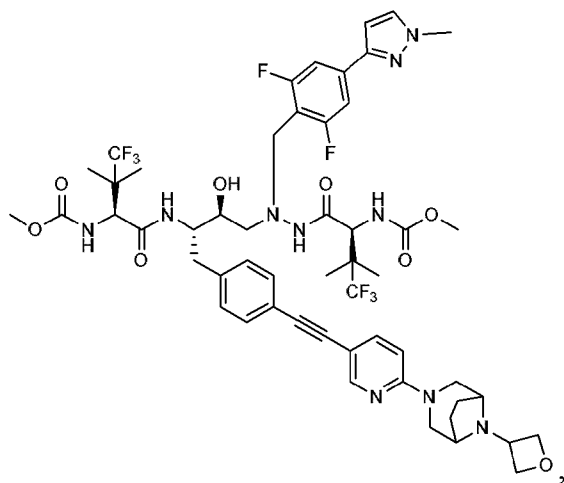
EXAMPLE 125



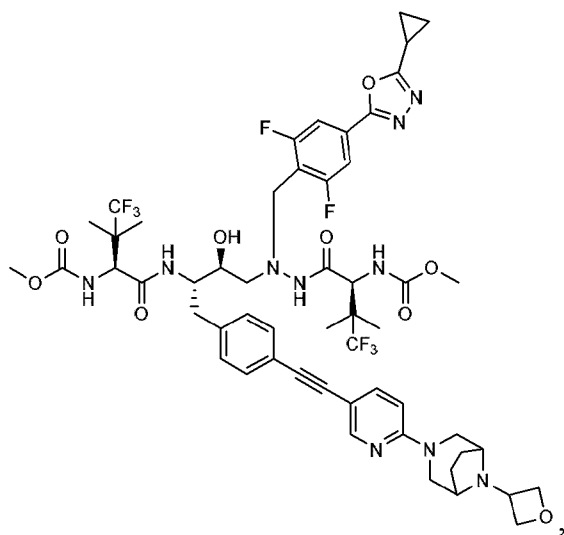
EXAMPLE 126



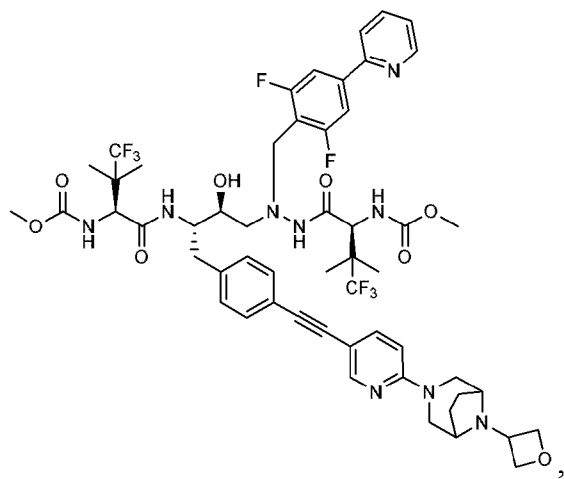
EXAMPLE 127



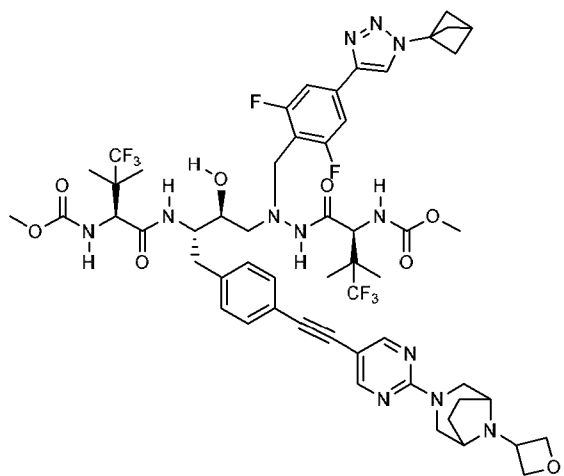
EXAMPLE 128



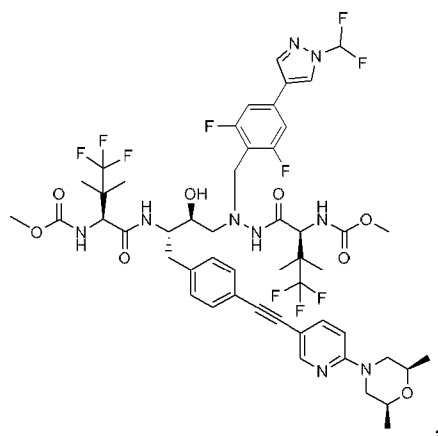
EXAMPLE 129



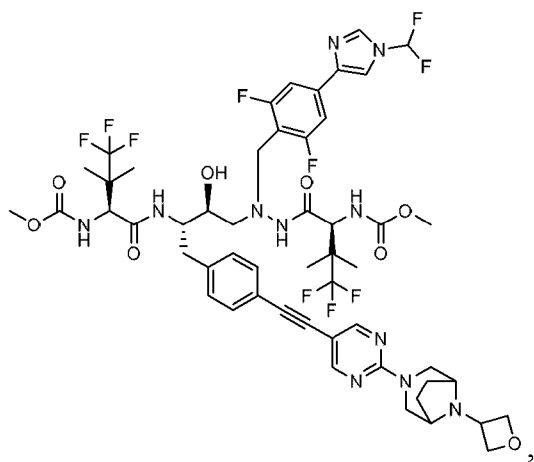
EXAMPLE 130



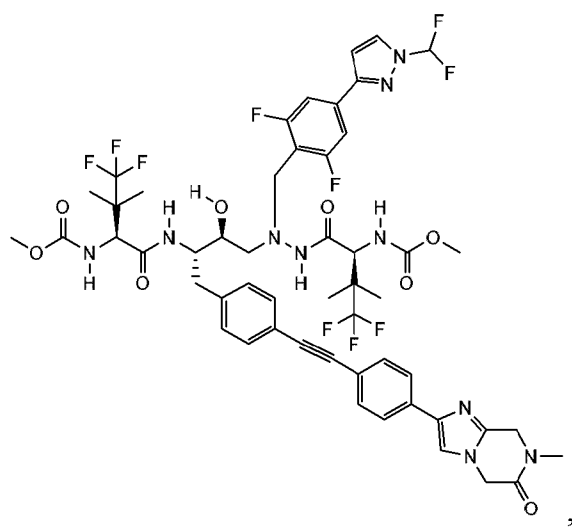
EXAMPLE 131



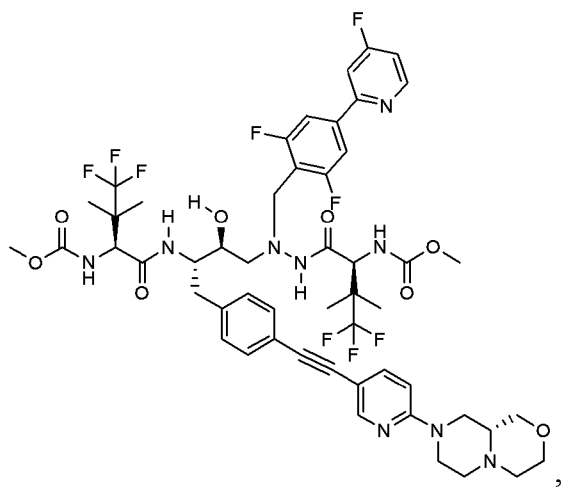
EXAMPLE 132



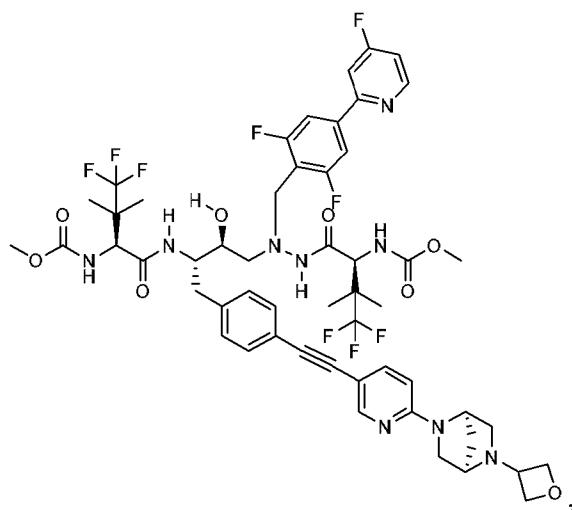
EXAMPLE 133



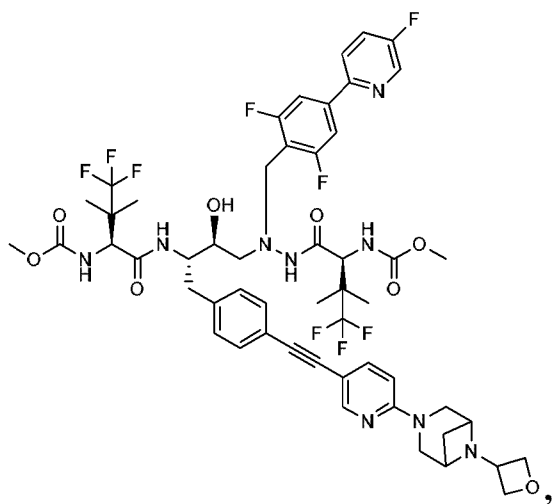
EXAMPLE 134



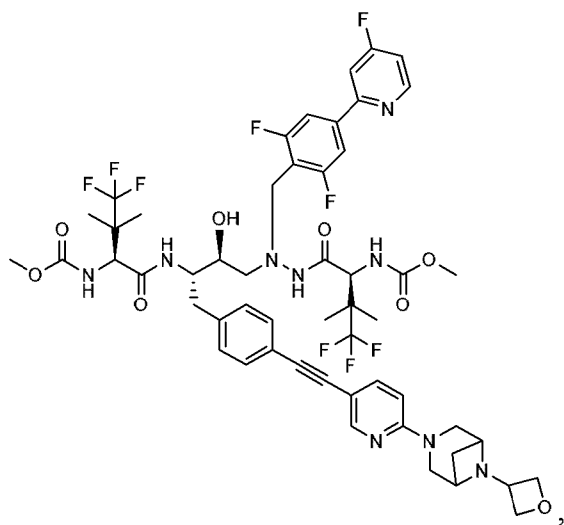
EXAMPLE 137



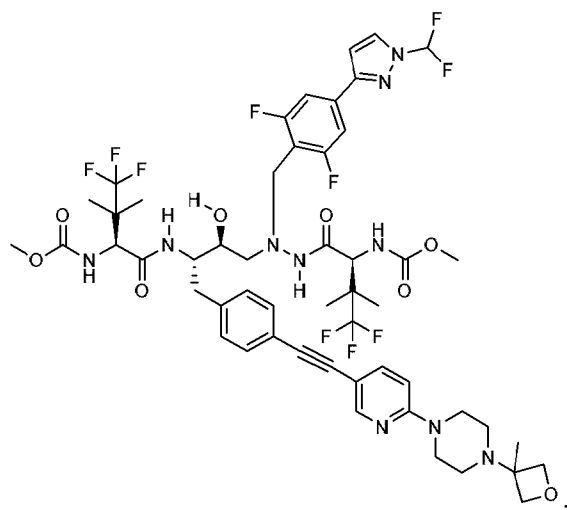
EXAMPLE 138



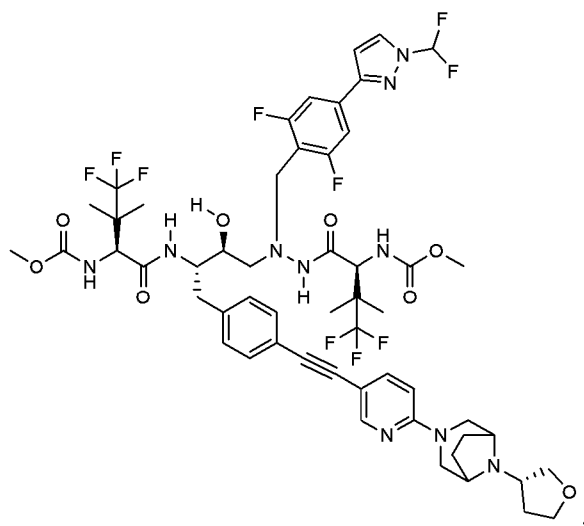
EXAMPLE 139



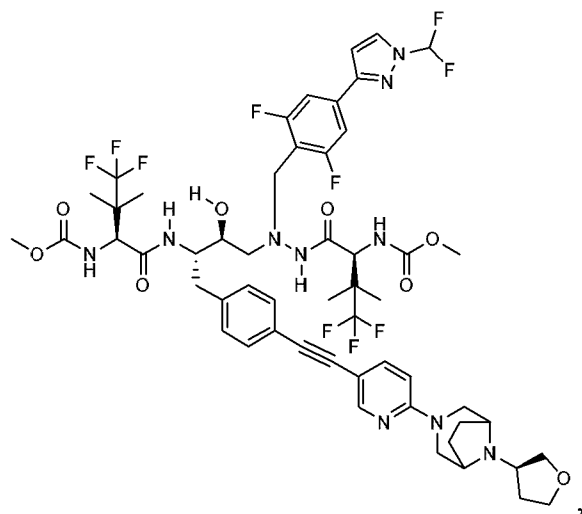
EXAMPLE 140



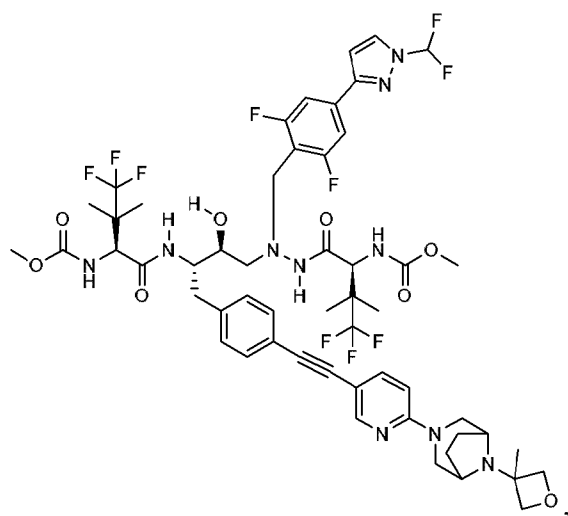
EXAMPLE 141



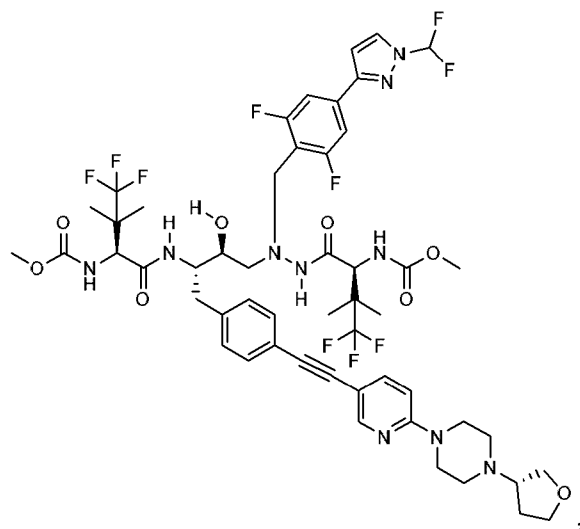
EXAMPLE 142



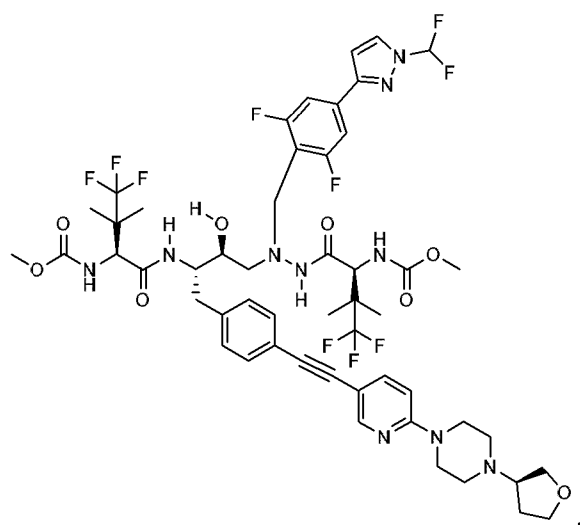
EXAMPLE 143



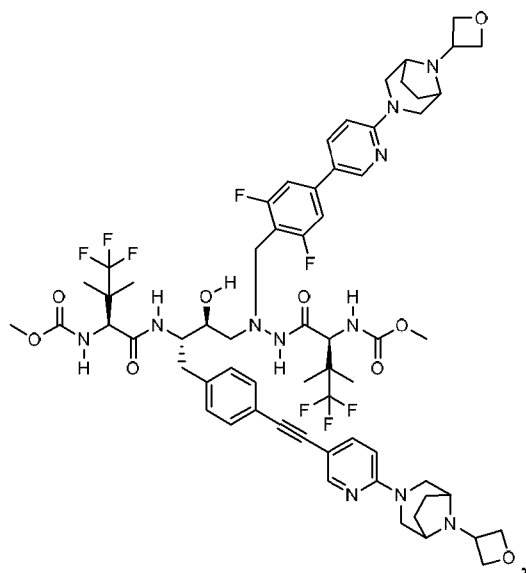
EXAMPLE 144



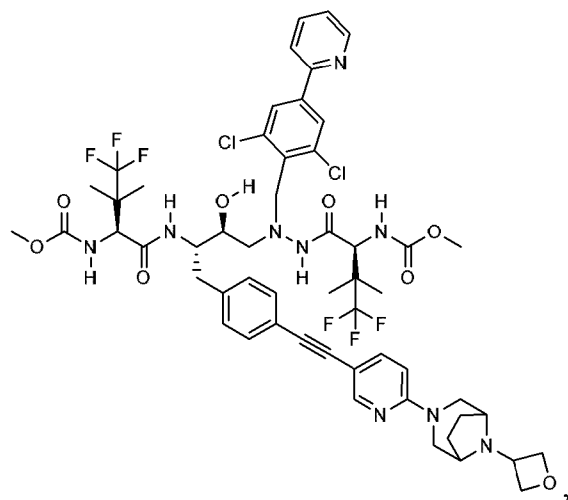
EXAMPLE 145



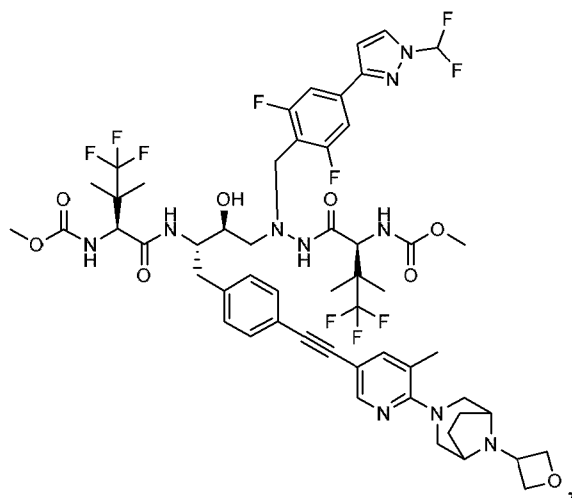
EXAMPLE 146



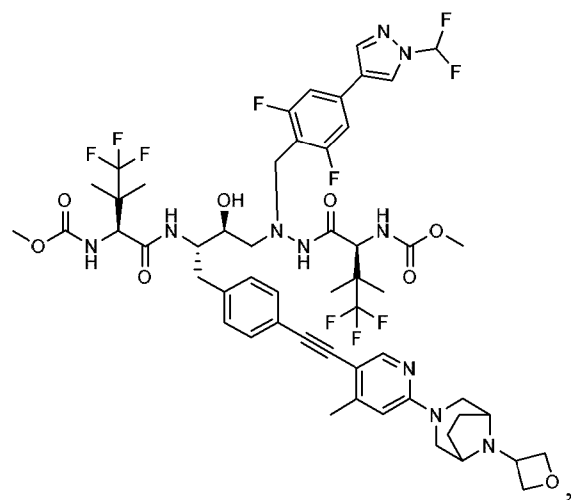
EXAMPLE 147



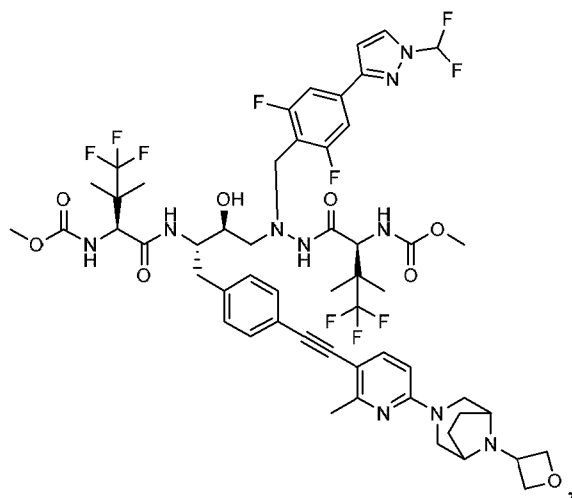
EXAMPLE 149



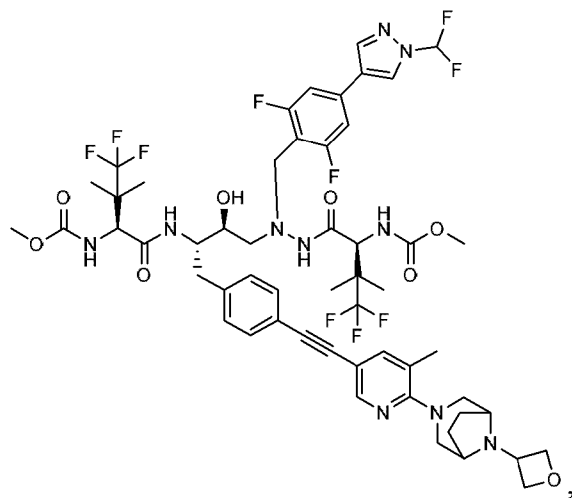
EXAMPLE 150



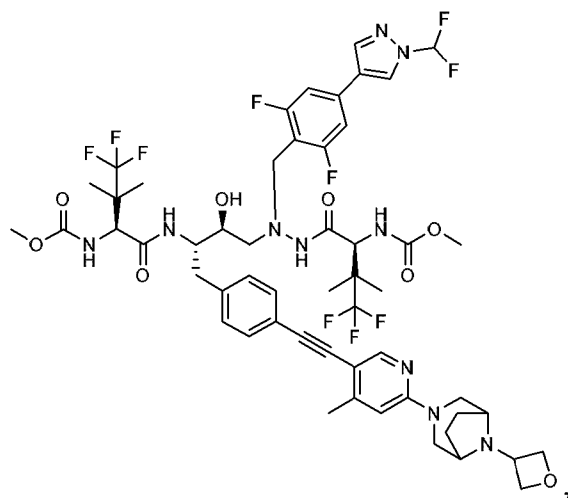
EXAMPLE 151



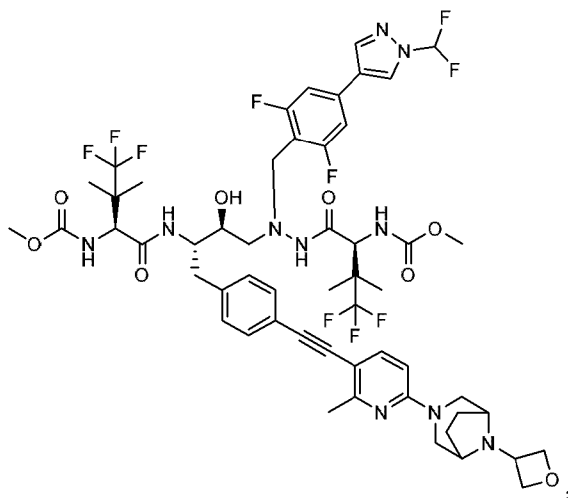
EXAMPLE 152



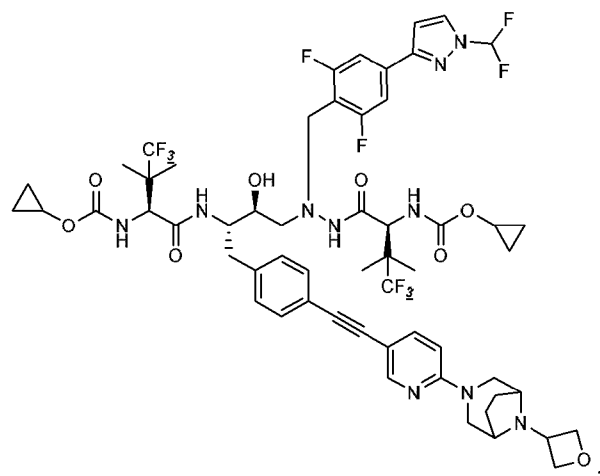
EXAMPLE 153



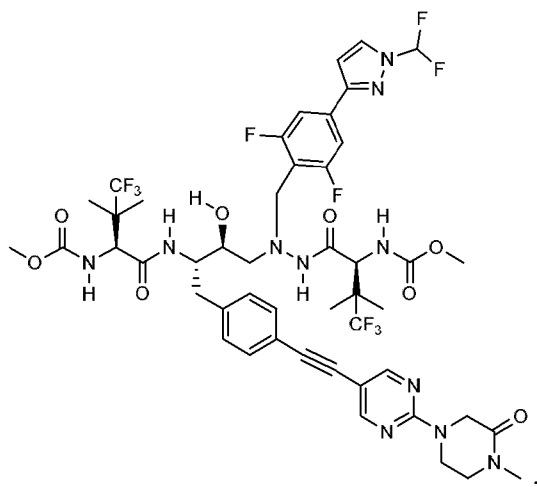
EXAMPLE 154



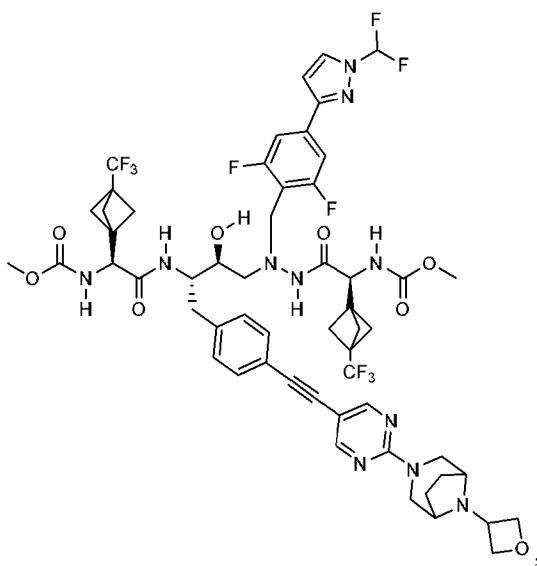
EXAMPLE 155



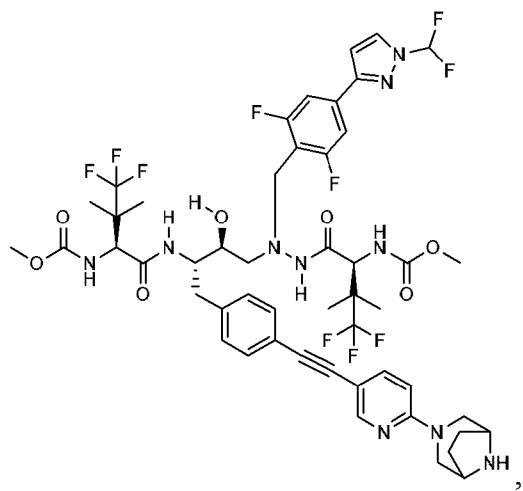
EXAMPLE 156



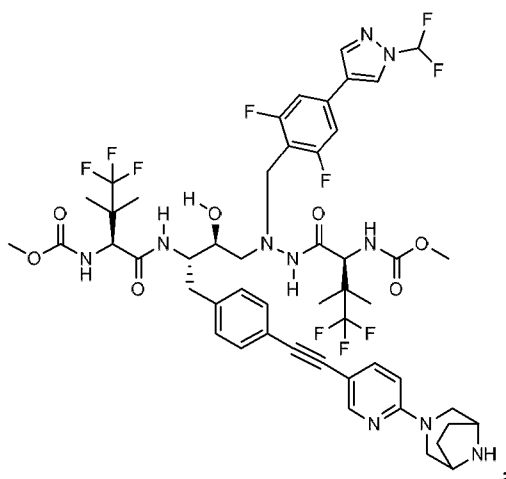
EXAMPLE 159



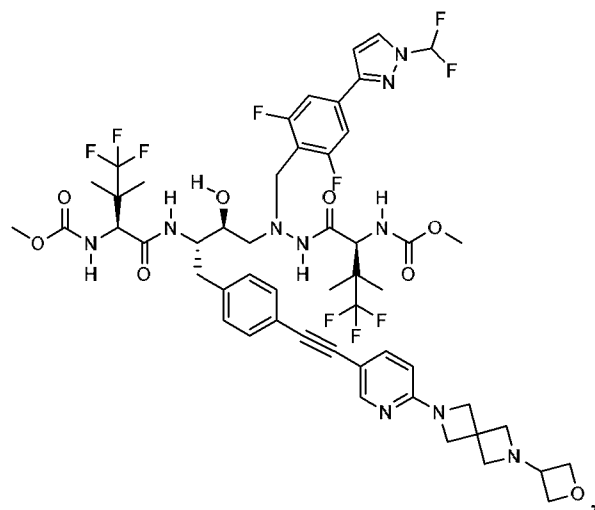
EXAMPLE 160



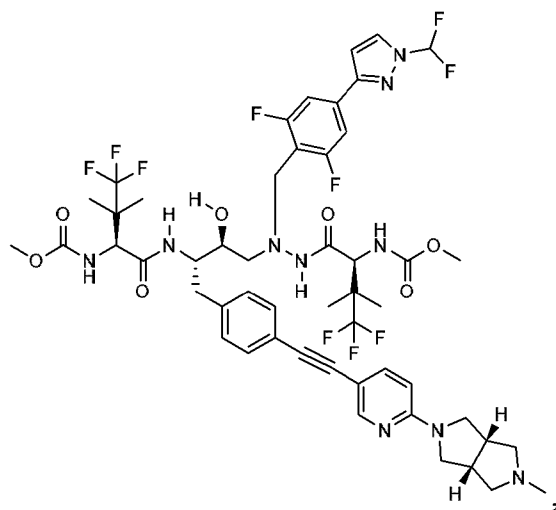
EXAMPLE 161



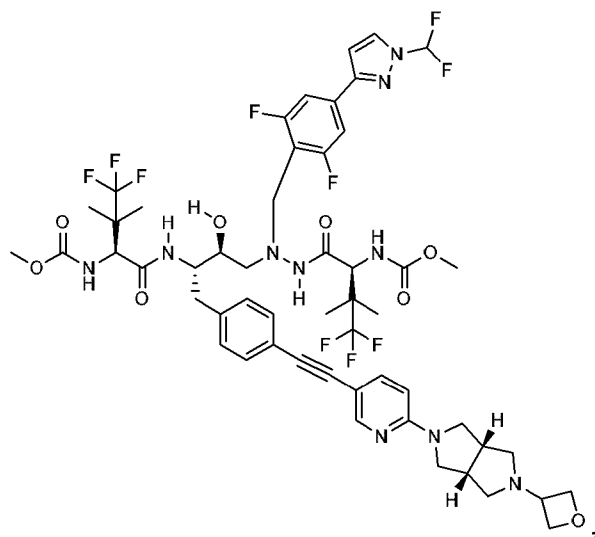
EXAMPLE 162



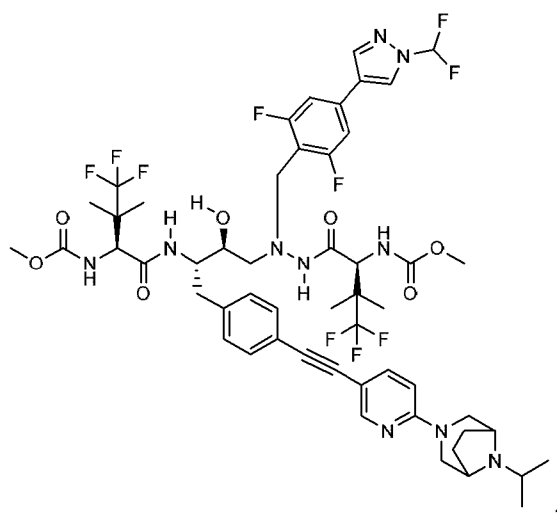
EXAMPLE 163



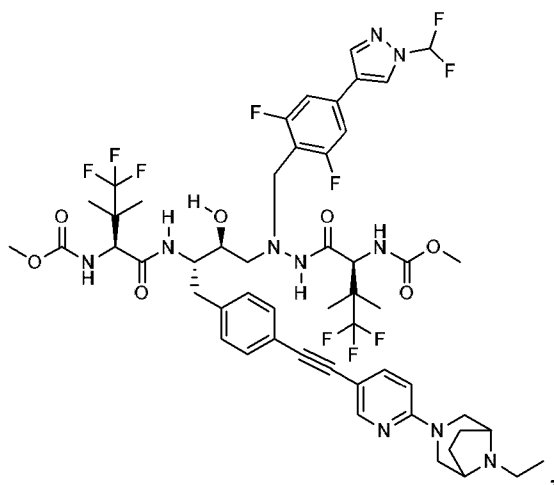
EXAMPLE 164



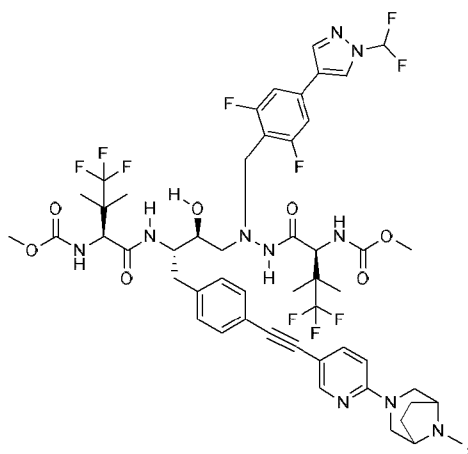
EXAMPLE 165



EXAMPLE 166



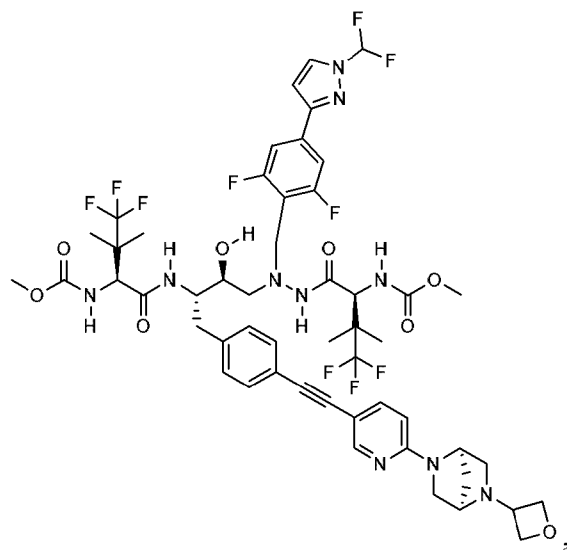
EXAMPLE 167



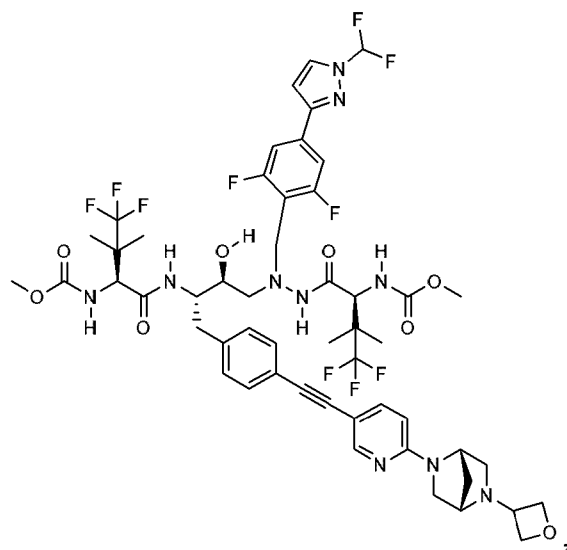
EXAMPLE 168



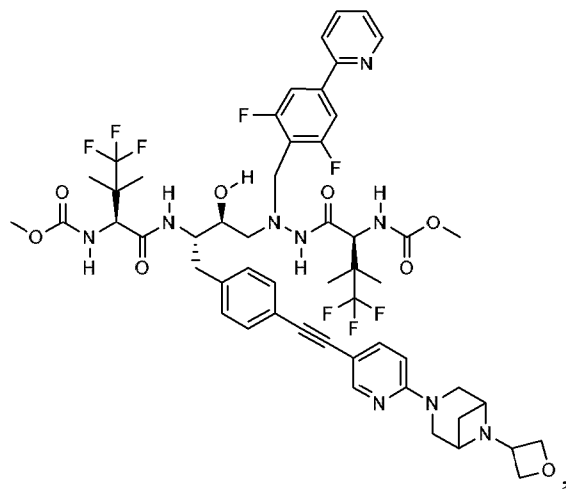




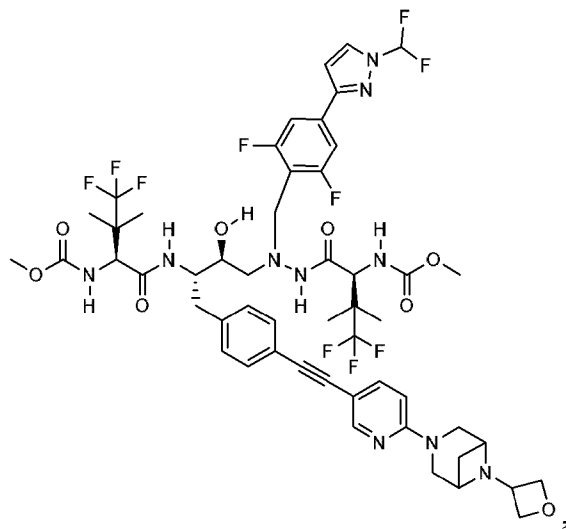
EXAMPLE 173



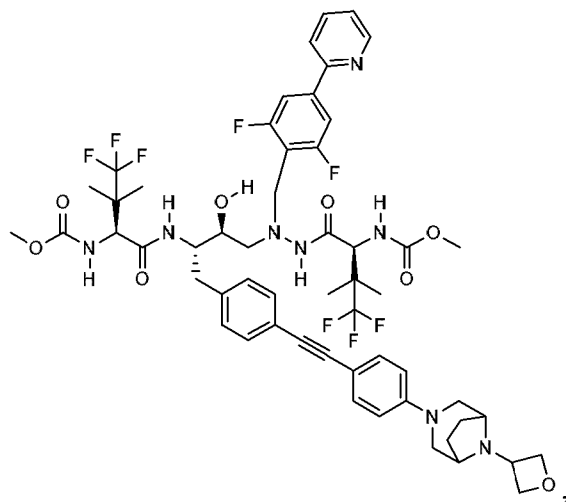
EXAMPLE 174



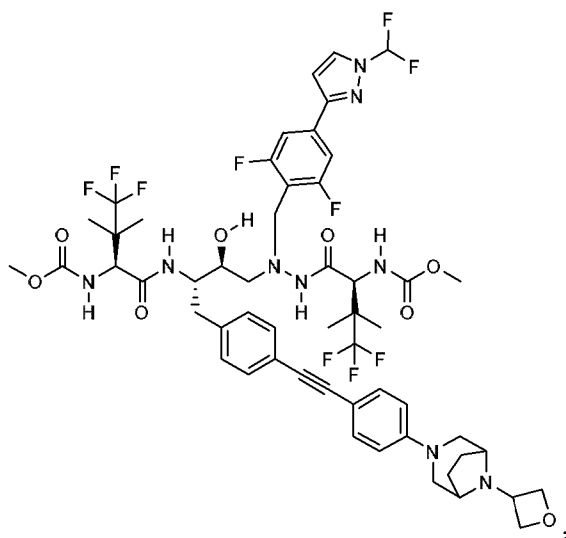
EXAMPLE 175



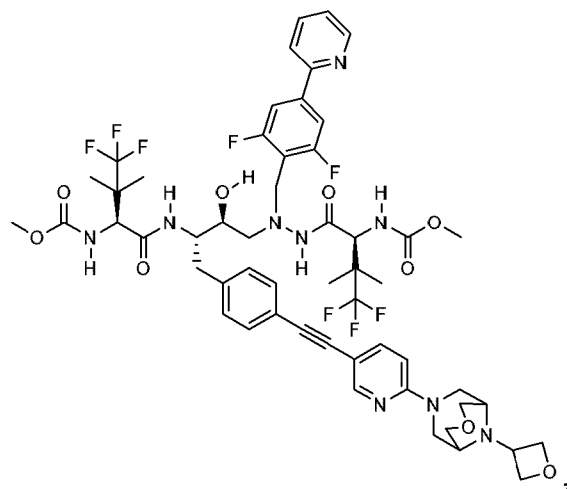
EXAMPLE 176



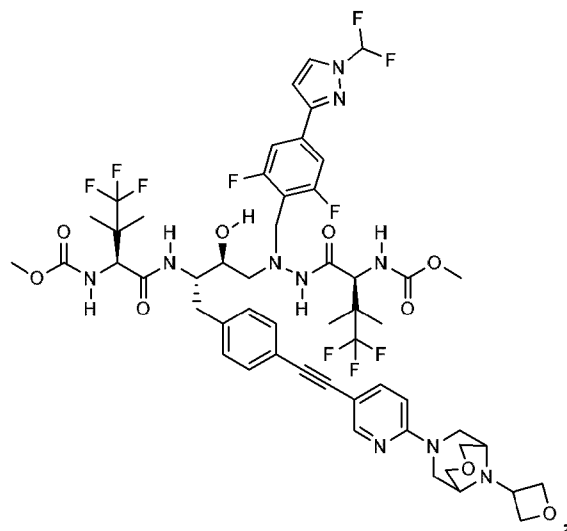
EXAMPLE 177



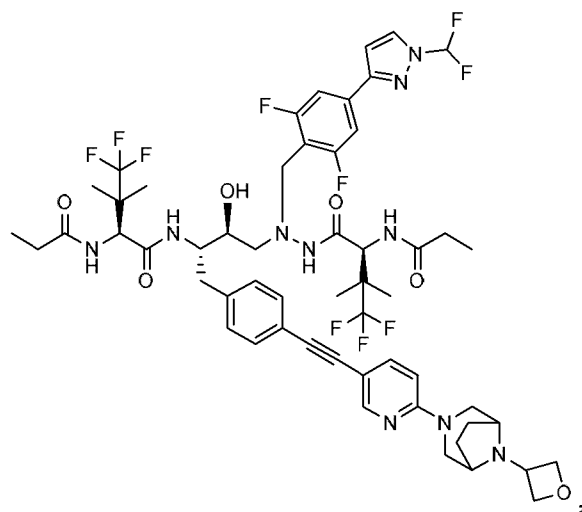
EXAMPLE 178



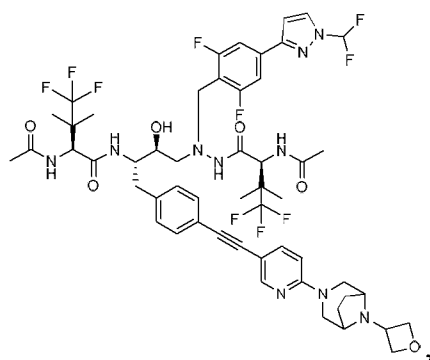
EXAMPLE 179



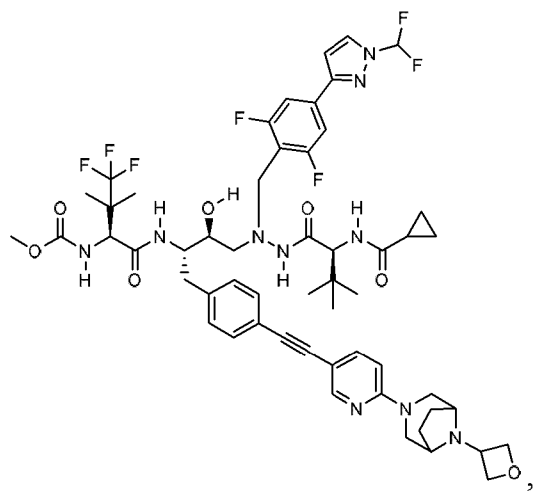
EXAMPLE 180



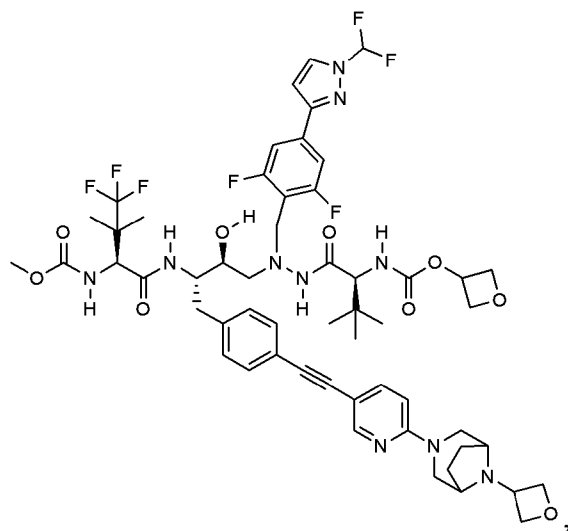
EXAMPLE 181



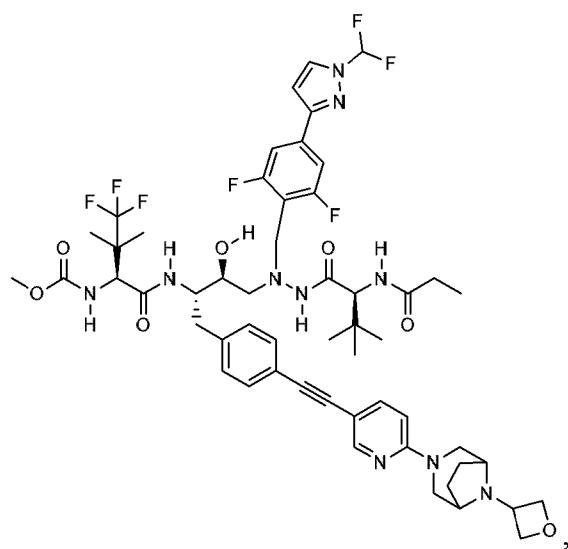
EXAMPLE 182



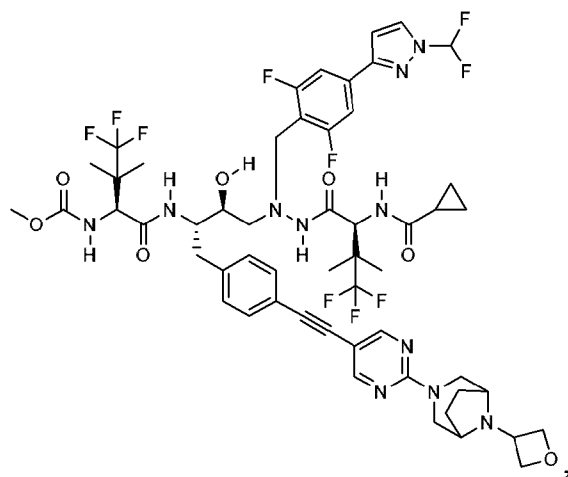
EXAMPLE 183



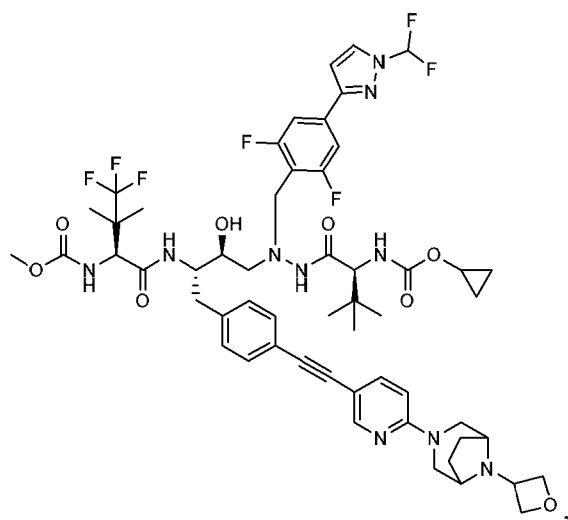
EXAMPLE 184



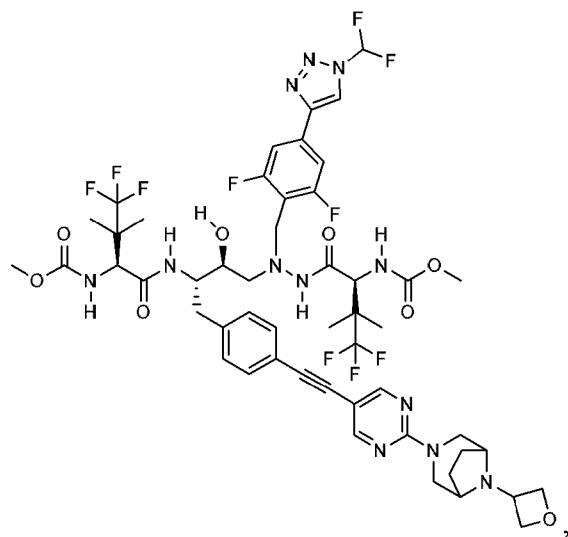
EXAMPLE 185



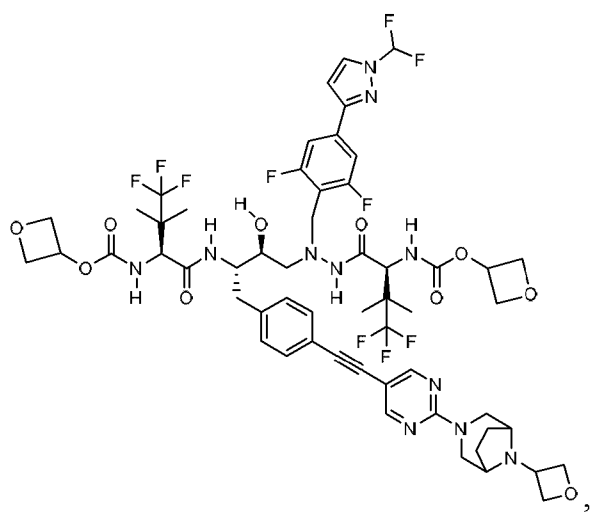
EXAMPLE 186



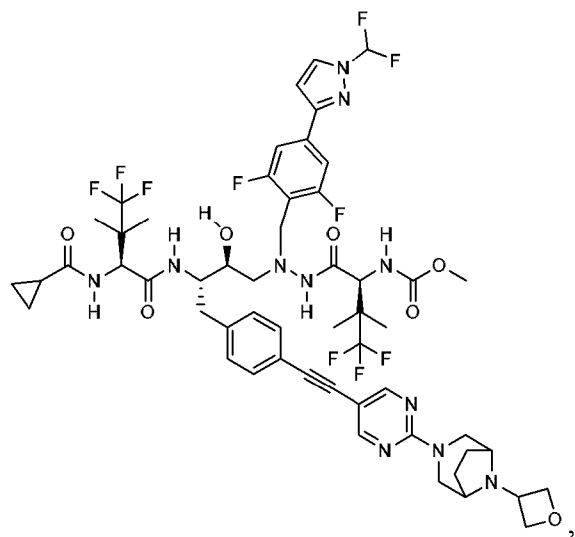
EXAMPLE 187



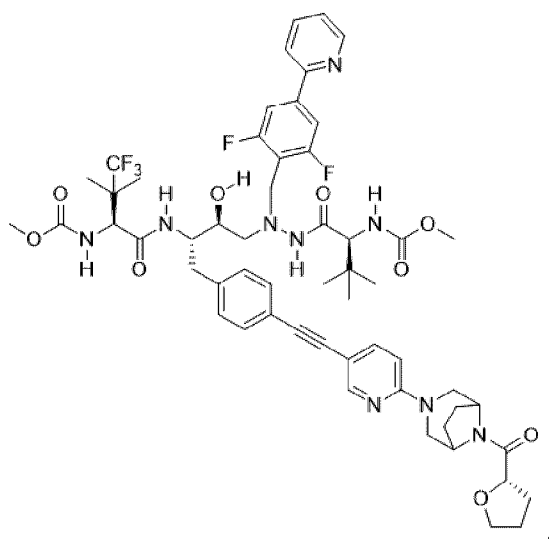
EXAMPLE 219



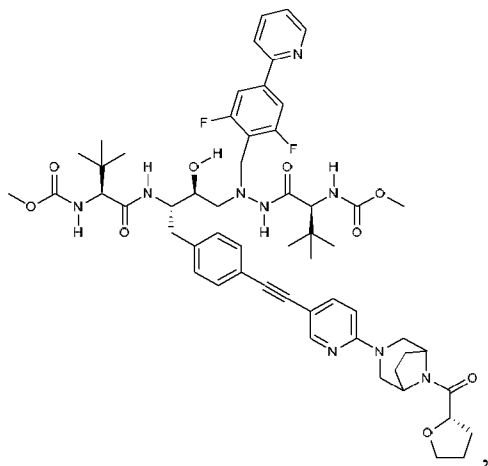
EXAMPLE 220



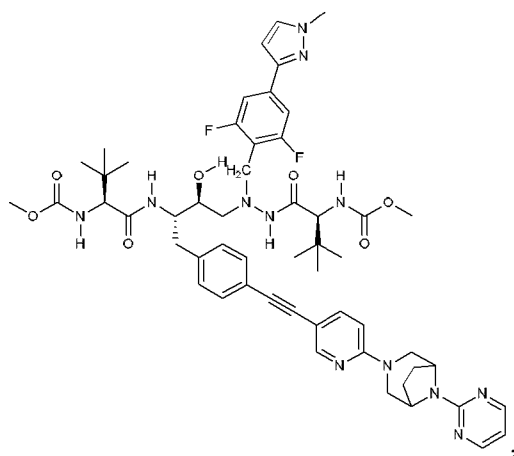
EXAMPLE 221



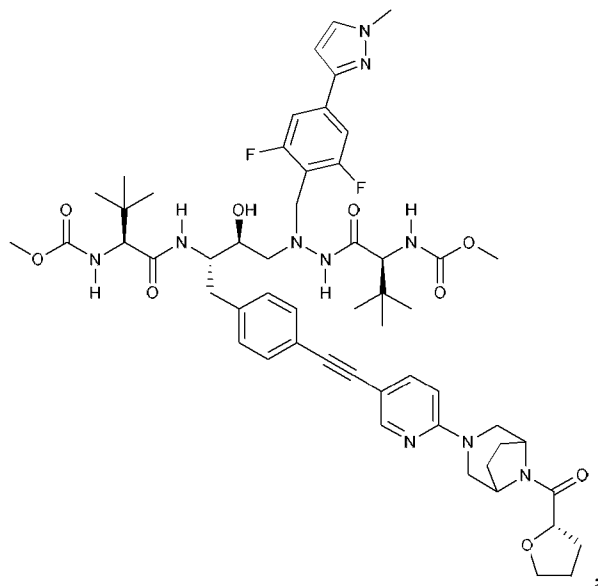
EXAMPLE 224



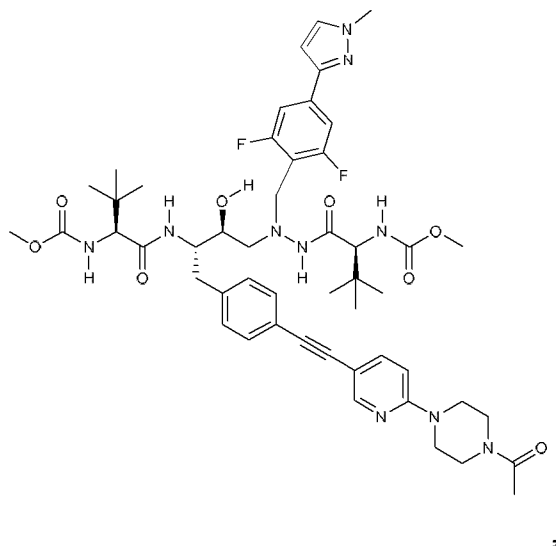
EXAMPLE 225



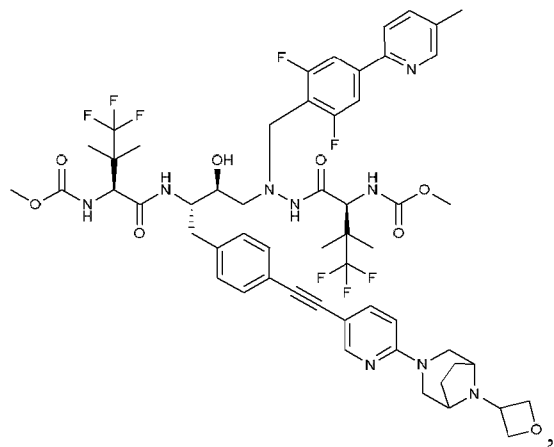
EXAMPLE 226



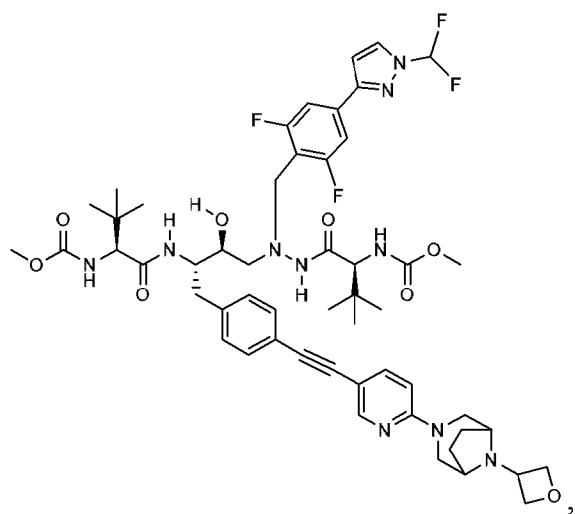
EXAMPLE 227



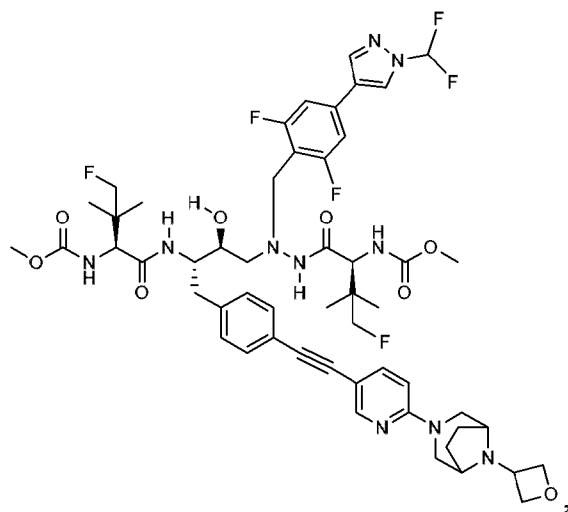
EXAMPLE 228



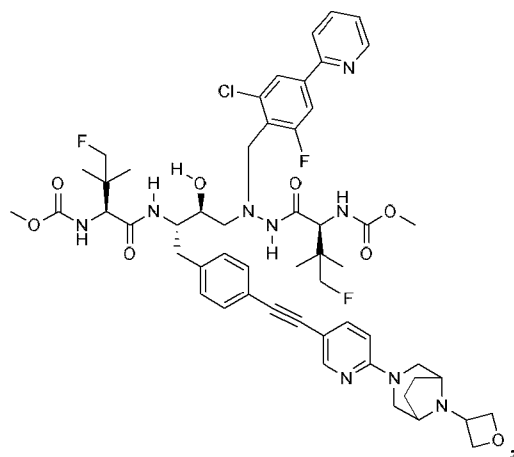
EXAMPLE 229



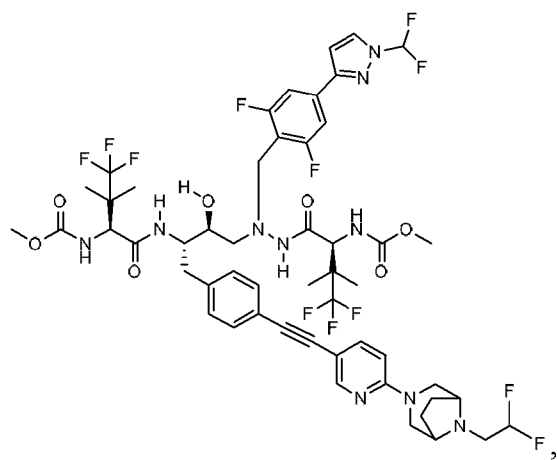
EXAMPLE 232



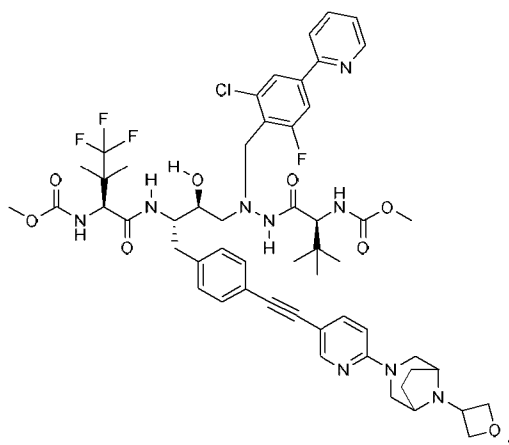
EXAMPLE 233



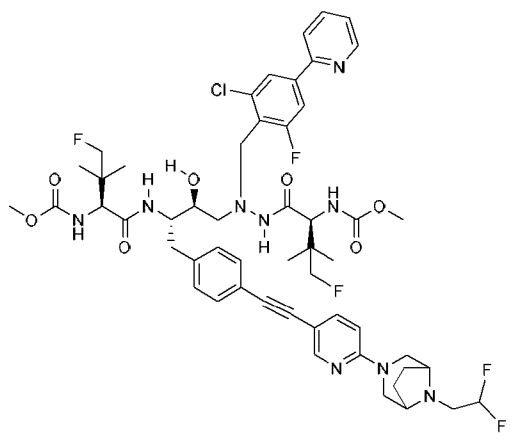
EXAMPLE 234



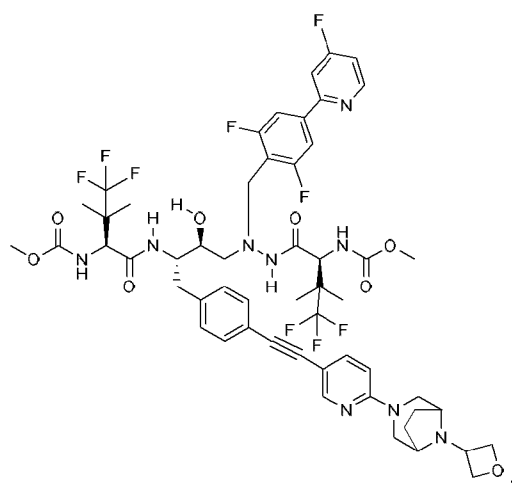
EXAMPLE 236



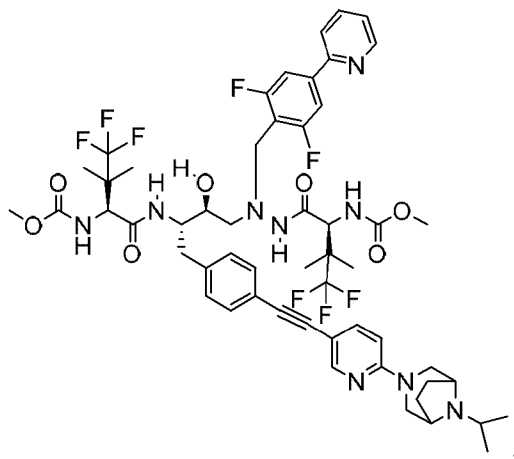
EXAMPLE 237



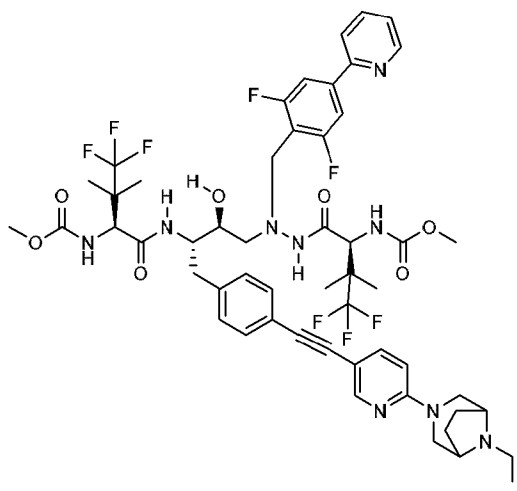
EXAMPLE 238



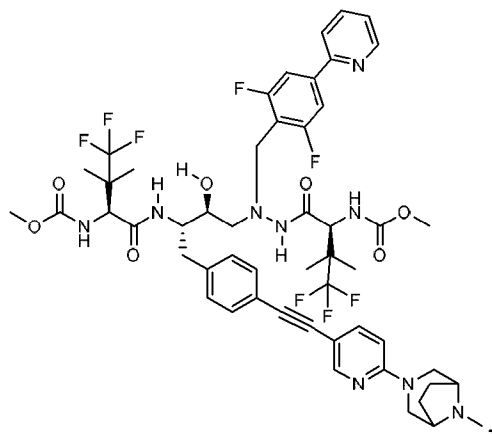
EXAMPLE 239



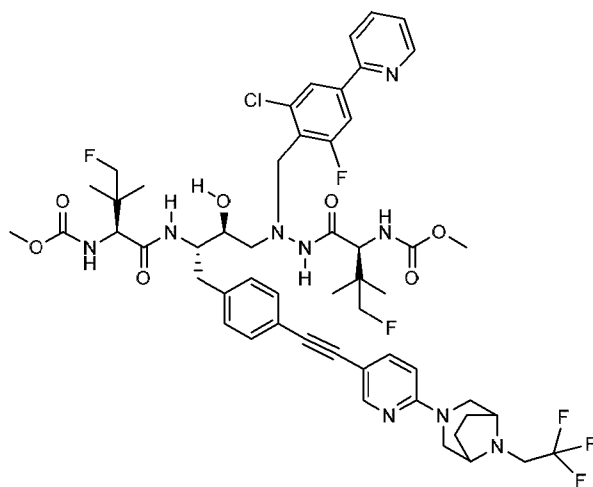
EXAMPLE 240



EXAMPLE 241

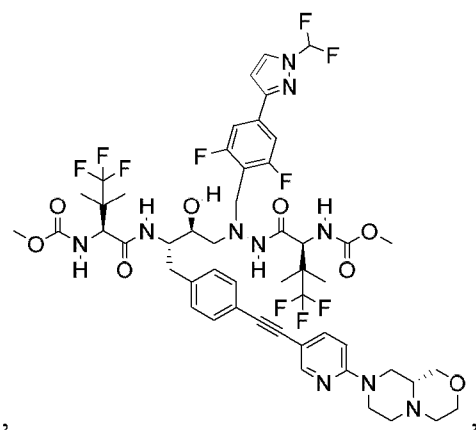
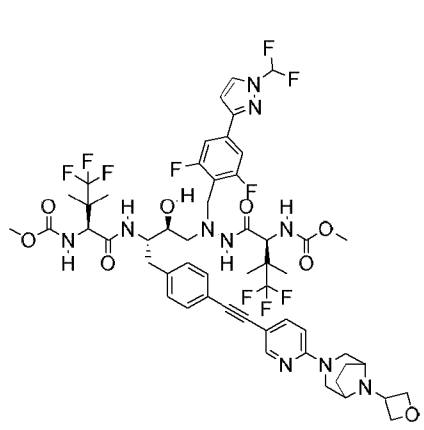
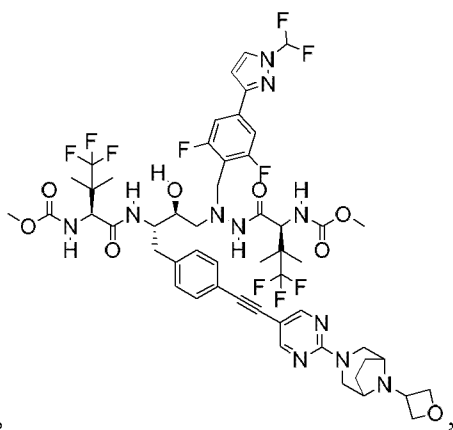
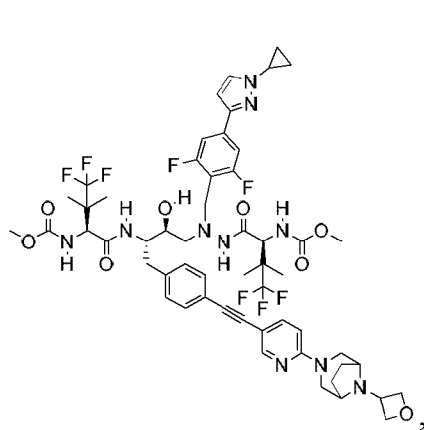
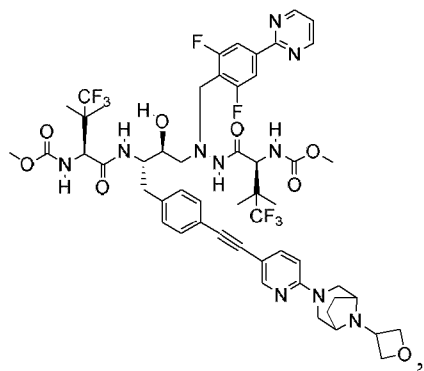


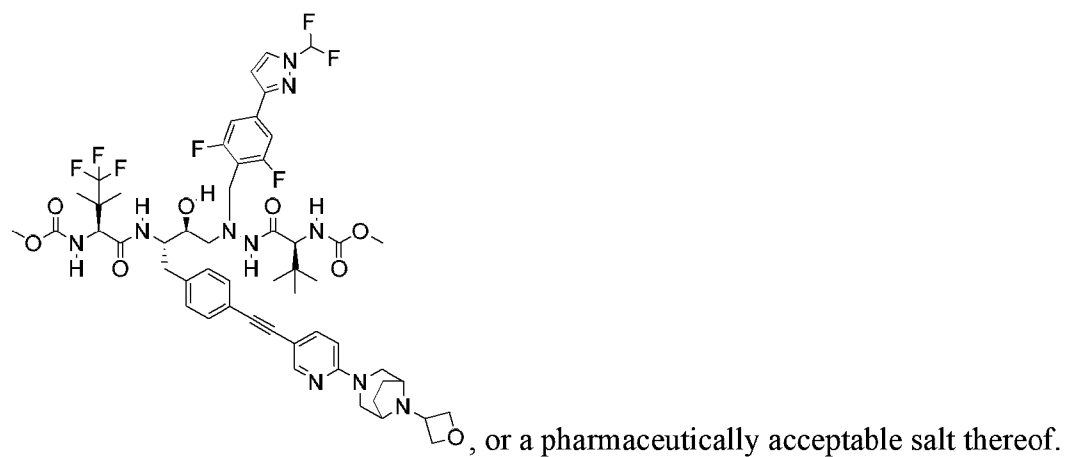
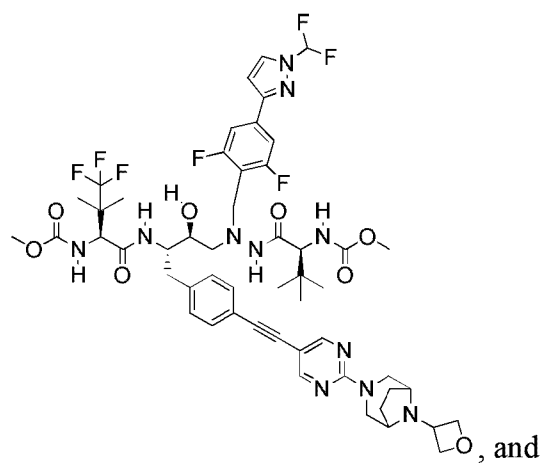
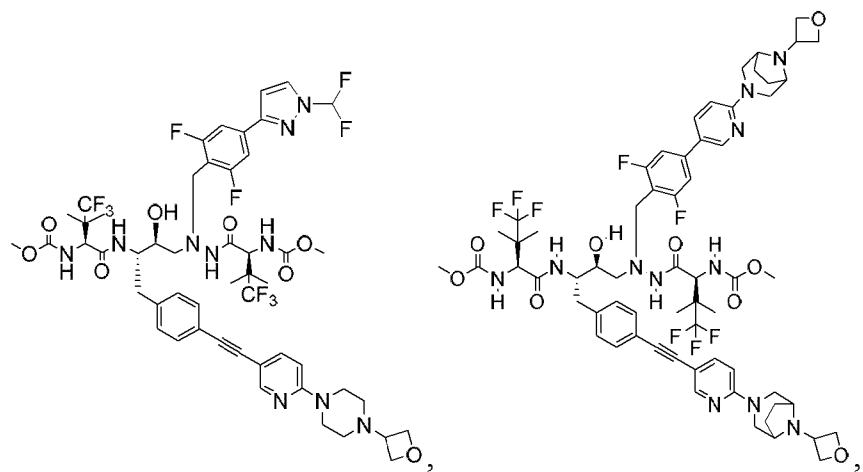
EXAMPLE 242, and



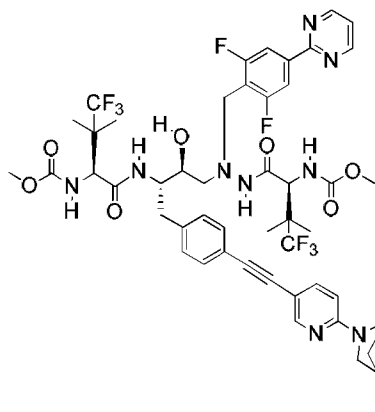
EXAMPLE 244.

37. The compound of any one of claims 1, 2 and 36, selected from:



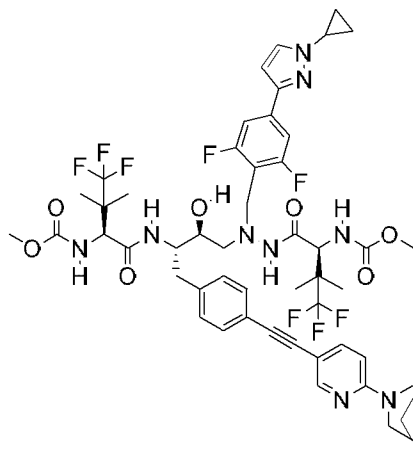


38. The compound of any one of claims 1, 2 and 36, which is



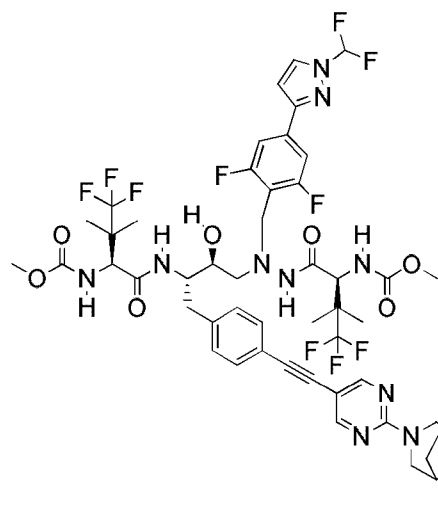
; or a pharmaceutically acceptable salt thereof.

39. The compound of any one of claims 1, 2 and 36, which is



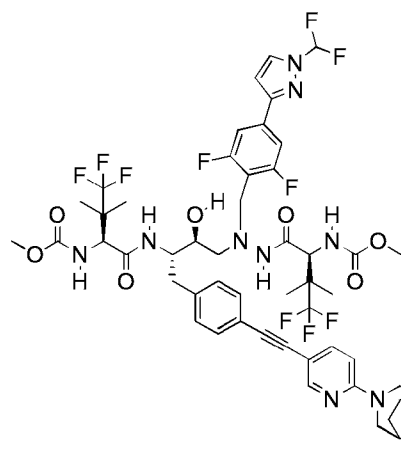
; or a pharmaceutically acceptable salt thereof.

40. The compound of any one of claims 1, 2 and 36, which is



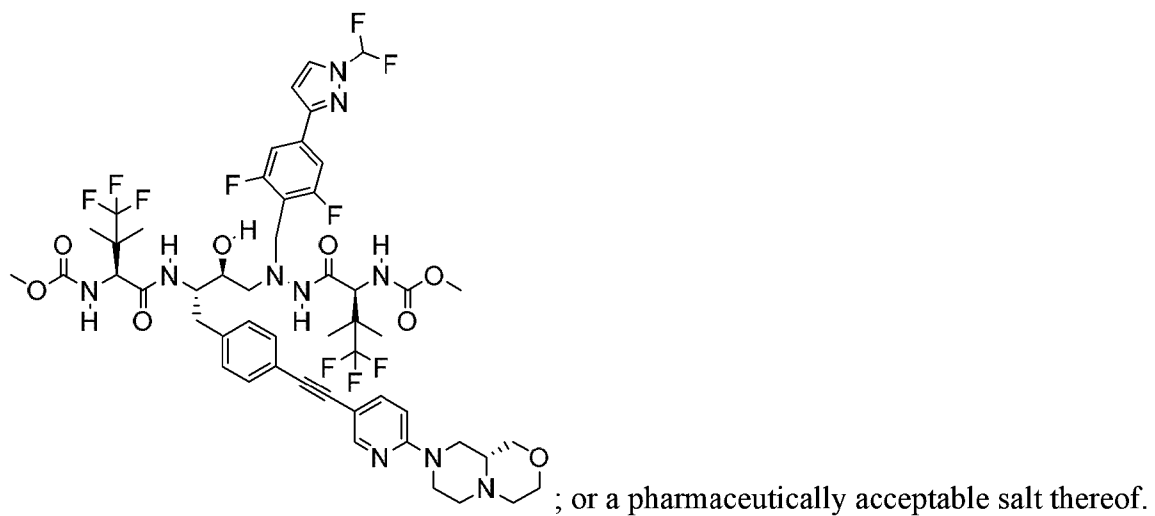
; or a pharmaceutically acceptable salt thereof.

41. The compound of any one of claims 1, 2 and 36, which is

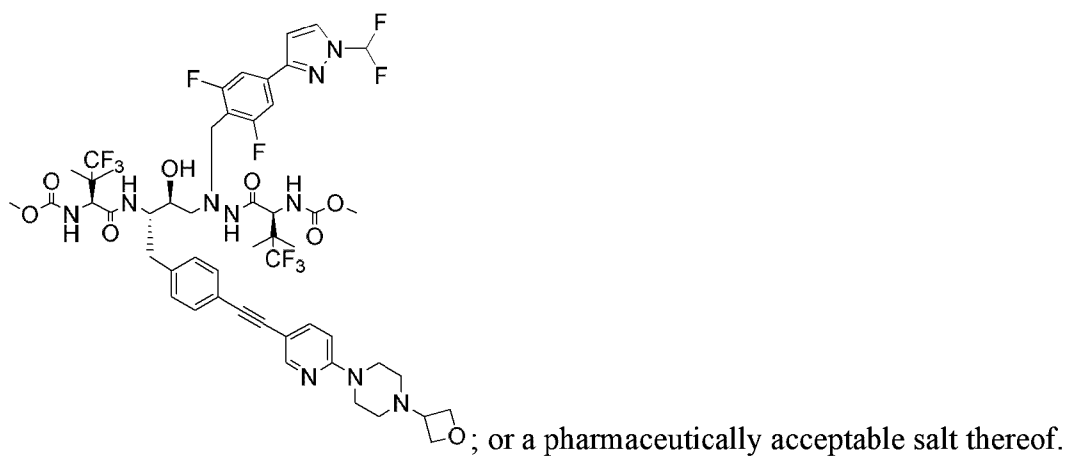


; or a pharmaceutically acceptable salt thereof.

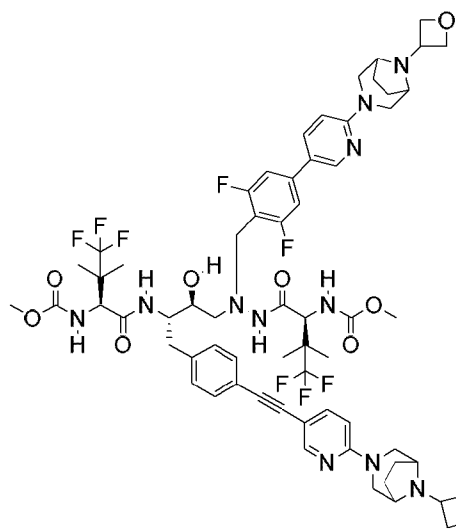
42. The compound of any one of claims 1, 2 and 36, which is



43. The compound of any one of claims 1, 2 and 36, which is

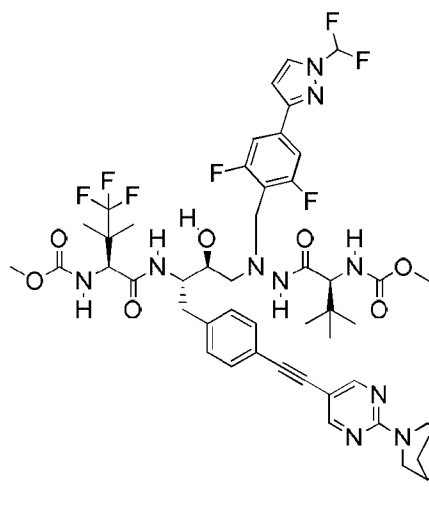


44. The compound of any one of claims 1, 2 and 36, which is



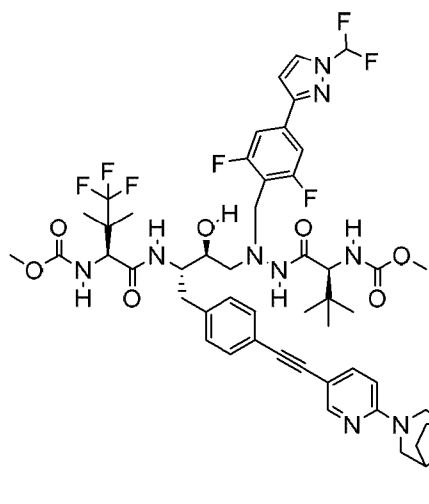
; or a pharmaceutically acceptable salt thereof.

45. The compound of any one of claims 1, 2 and 36, which is

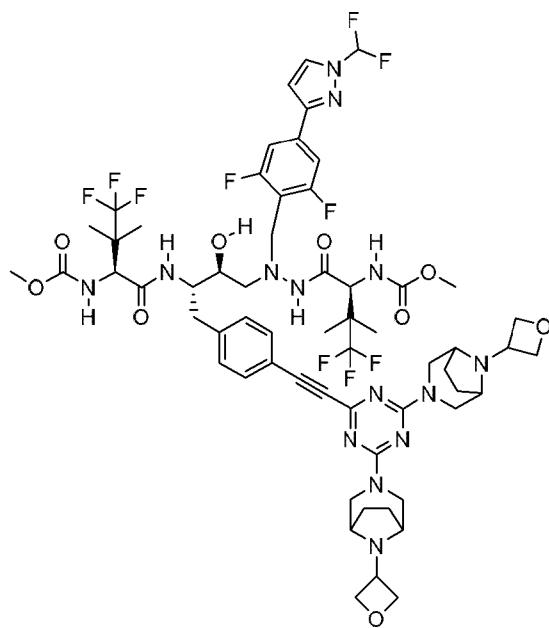


; or a pharmaceutically acceptable salt thereof.

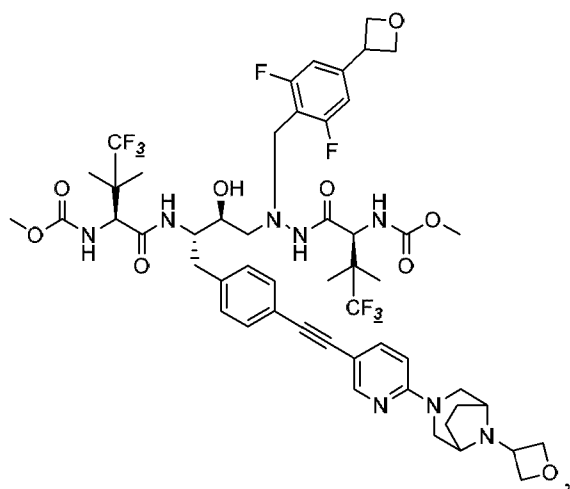
46. The compound of any one of claims 1, 2 and 36, which is



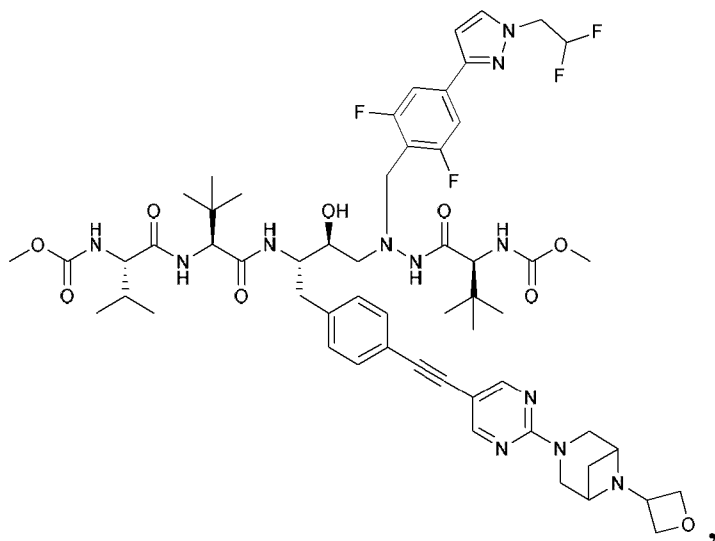
47. A compound of any of Examples 49, 83, 222, and 223 or a pharmaceutically acceptable salt thereof:



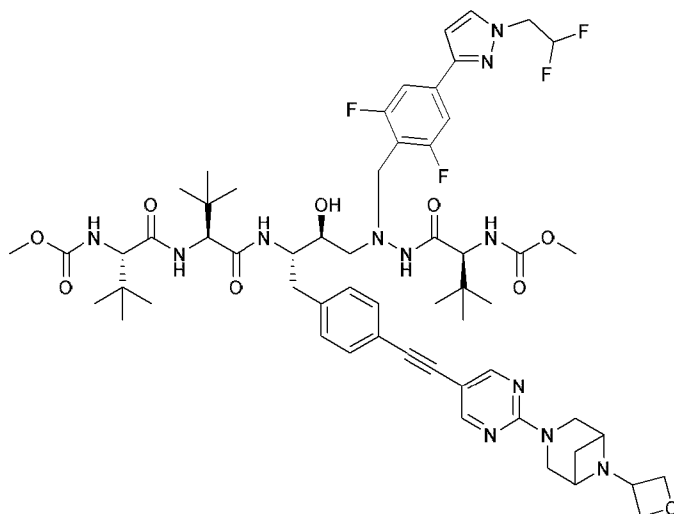
EXAMPLE 49



EXAMPLE 83



EXAMPLE 222, and



48. A pharmaceutical composition comprising a compound of any one of claims 1 to 47, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

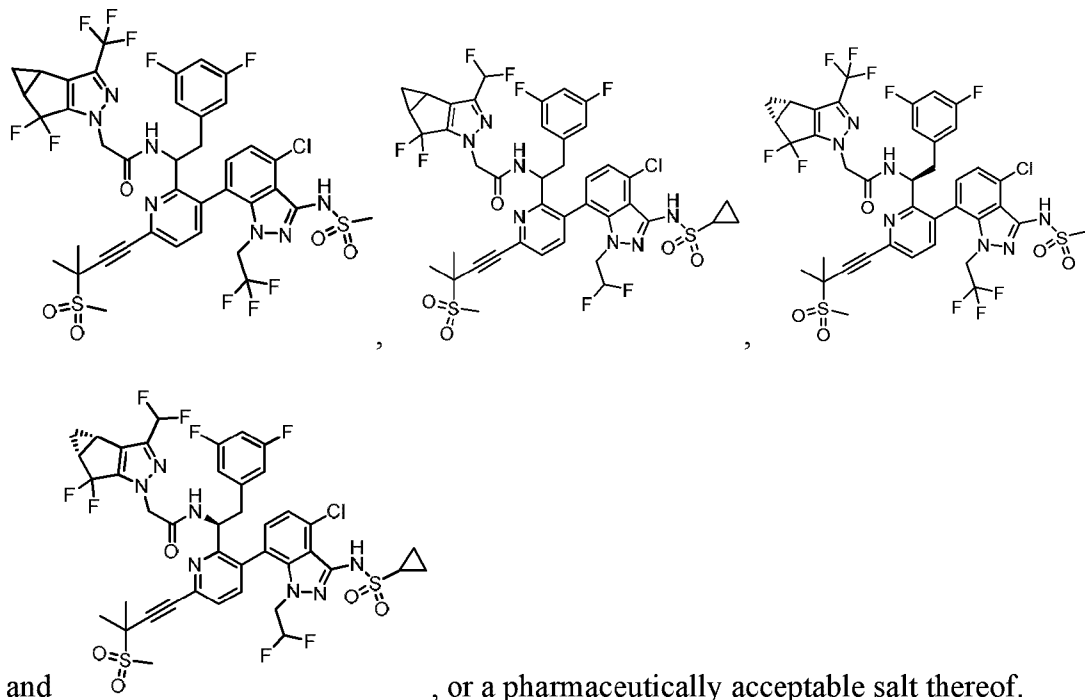
infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof.

51. The pharmaceutical composition of claim 49, wherein the additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and pharmacokinetic enhancers, or any combinations thereof.

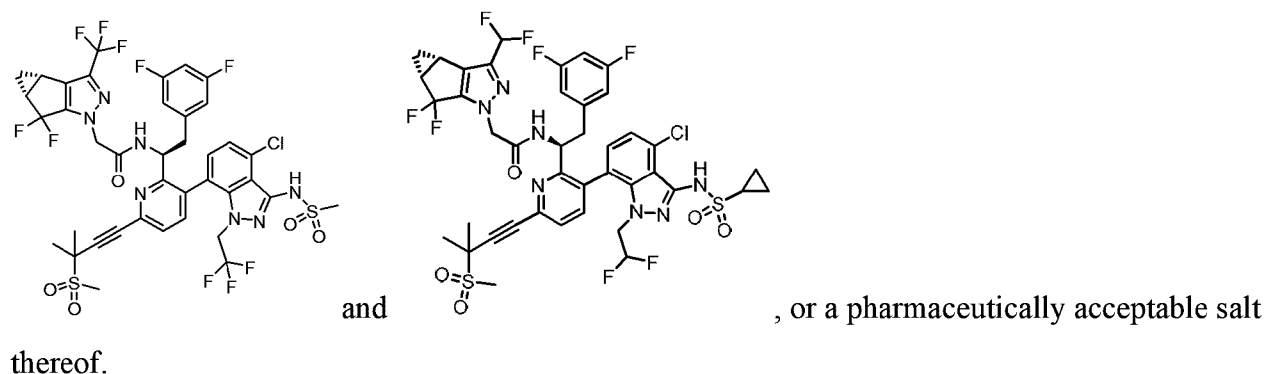
52. The pharmaceutical composition of any one of claims 49 to 51, wherein the additional therapeutic agents are selected from the group consisting of abacavir sulfate, bictegrovir, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate.

53. The pharmaceutical composition of any one of claims 49 to 52, wherein the additional therapeutic agents are selected from the group consisting of tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate.

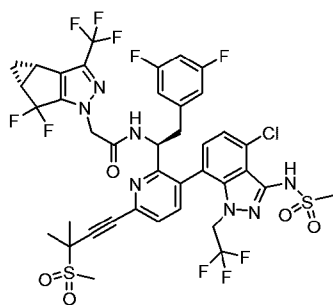
54. The pharmaceutical composition of any one of claims of 49 to 51, wherein the additional therapeutic agents are selected from the group consisting of:



55. The pharmaceutical composition of any one of claims 49 to 51, or 54, wherein the additional therapeutic agents are selected from the group consisting of:

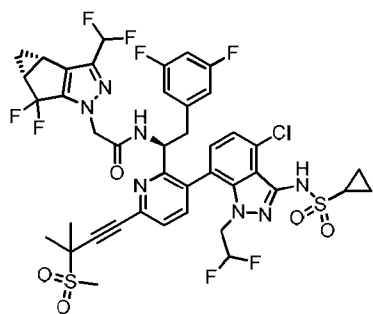


56. The pharmaceutical composition of any one of claims 49 to 51, or 54 to 55, wherein the additional therapeutic agent is:



, or a pharmaceutically acceptable salt thereof.

57. The pharmaceutical composition of any one of claims 49 to 51, or 54 to 56, wherein the additional therapeutic agent is:



, or a pharmaceutically acceptable salt thereof.

58. The pharmaceutical composition of any one of claims 49 to 51, wherein the additional therapeutic agents are selected from the group consisting of abacavir sulfate, bictegravir, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, tenofovir alafenamide hemifumarate, emtricitabine, lamivudine, GS-9131, dolutegravir, and cabotegravir.

59. The pharmaceutical composition of any one of claims 49 to 51, or 58, wherein the additional therapeutic agents are selected from the group consisting of bictegravir, emtricitabine, and GS-9131.

60. The compound, or pharmaceutically acceptable salt thereof of any one of claims 1 to 47, for use in the treatment of a human immunodeficiency virus (HIV) infection.

61. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 47, for use in the manufacture of a medicament for the treatment of a human immunodeficiency virus (HIV) infection.

62. The pharmaceutical composition of any one of claims 48 to 59, for use in the treatment of a human immunodeficiency virus (HIV) infection.

63. The pharmaceutical composition of any one of claims 48 to 59, for use in the manufacture of a medicament for the treatment of a human immunodeficiency virus (HIV) infection.

64. The compound or pharmaceutically acceptable salt thereof of claim 60 or 61, wherein the compound or pharmaceutically acceptable salt thereof, is for use in combination with one, two, three, or four additional therapeutic agents as defined in any one of claims 50 to 59.

65. The compound or pharmaceutically acceptable salt thereof of claim 64, wherein the additional therapeutic agents are for simultaneous use with the compound or pharmaceutically acceptable salt thereof.

66. The compound or pharmaceutically acceptable salt thereof of claim 64, wherein the compound or pharmaceutically acceptable salt thereof, is combined with the additional therapeutic agents in a unitary dosage form for simultaneous use.

67. The compound or pharmaceutically acceptable salt thereof of claim 64, wherein the compound or pharmaceutically acceptable salt thereof, and the additional therapeutic agents are for sequentially use.

68. Use of the compound or pharmaceutically acceptable salt thereof of any one of claims 1 to 47, or the pharmaceutical composition of any one of claims 48 to 59, for the manufacture of a medicament for the treatment of a human immunodeficiency virus (HIV) infection.

69. Use of the compound or pharmaceutically acceptable salt thereof of any one of claims 1 to 47, or the pharmaceutical composition of any one of claims 48 to 59, for the treatment of a human immunodeficiency virus (HIV) infection.

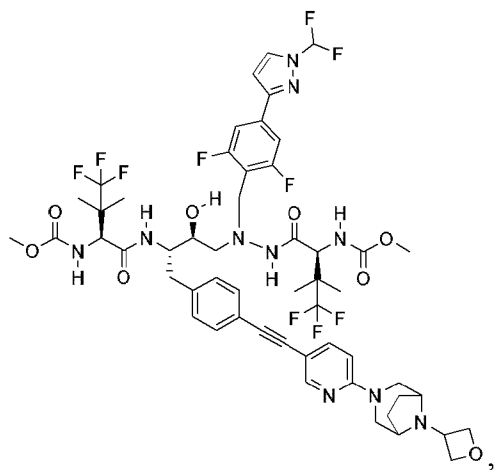
70. The use of claim 68 or 69, wherein the compound or pharmaceutically acceptable salt thereof, is for use in combination with one, two, three, or four additional therapeutic agents as defined in any one of claims 50 to 59.

71. The use of claim 70, wherein the additional therapeutic agents are for simultaneous use with the compound or pharmaceutically acceptable salt thereof.

72. The use of claim 70, wherein the compound or pharmaceutically acceptable salt thereof, is combined with the additional therapeutic agents in a unitary dosage form for simultaneous use.

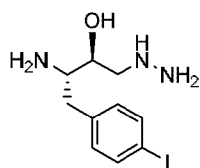
73. The use as claimed in claim 70, wherein the compound or pharmaceutically acceptable salt thereof and the additional therapeutic agents are for sequential use.

74. A process for preparing compound:

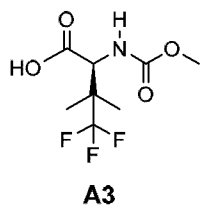


or a pharmaceutically acceptable salt thereof, comprising:

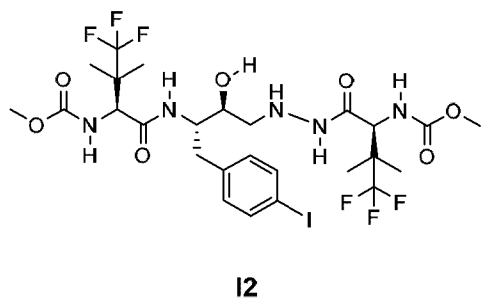
a) reacting deprotected Compound I2a:



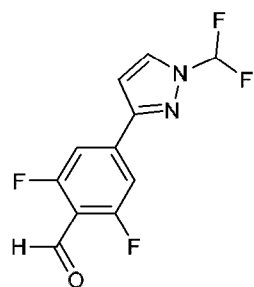
with Compound A3:



to provide Compound I2:

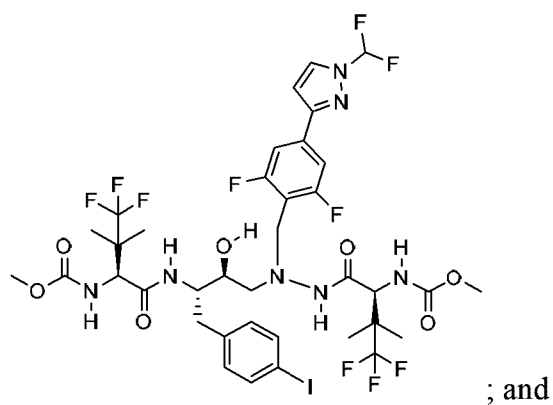


b) reacting Compound I2 with Compound P4:

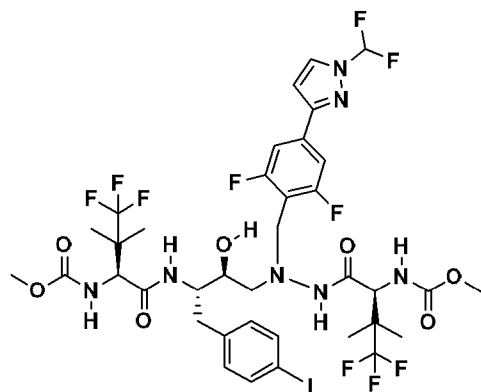


P4

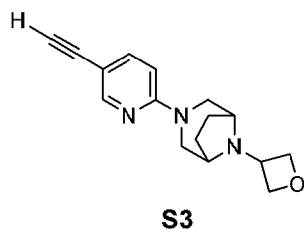
to provide a compound of structure:



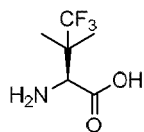
c) reacting a compound of structure:



with Compound S3:

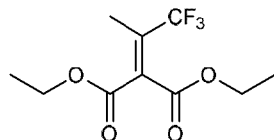


75. The process of claim 74, wherein Compound A3 is prepared by a process comprising reacting methyl chloroformate with deprotected Compound A1 having the structure:



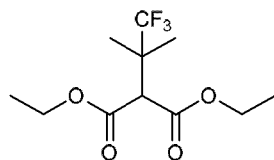
76. The process of claim 75, wherein deprotected Compound A1 is prepared by a process comprising:

- a) reacting Compound A1a:



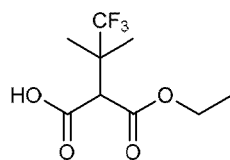
A1a

with methylmagnesium iodide to provide Compound A1b:



A1b

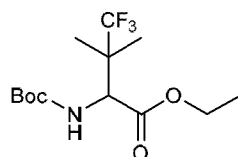
- b) reacting Compound A1b with NaOH to provide Compound A1c:



A1c

;

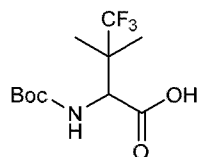
c) reacting Compound A1c with diphenylphosphoryl azide (DPPA), triethylamine and t-BuOH to provide Compound A1d:



A1d

;

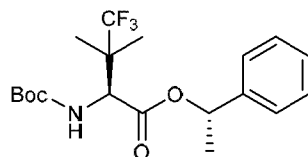
d) reacting Compound A1d with LiOH to provide Compound A1e:



A1e

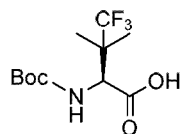
;

e) coupling of Compound A1e with (S)-(-)-1-phenylethanol to provide Compound A1f:



A1f

f) reacting Compound A1f with hydrogen to provide Compound A1:

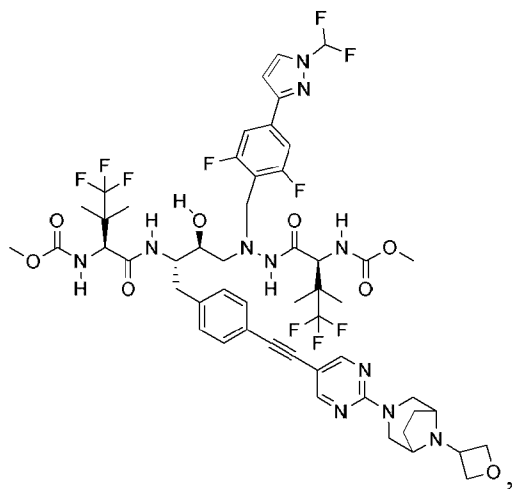


A1

; and

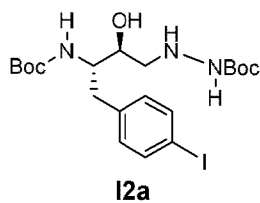
g) deprotecting Compound A1 with HCl.

77. A process for preparing compound:

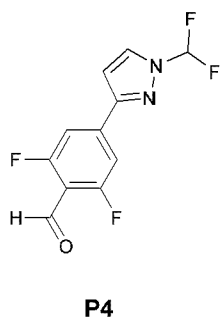


or a pharmaceutically acceptable salt thereof, comprising:

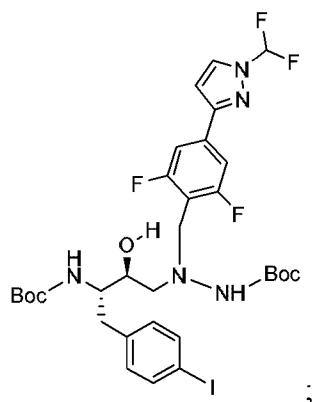
a) reacting Compound I2a:



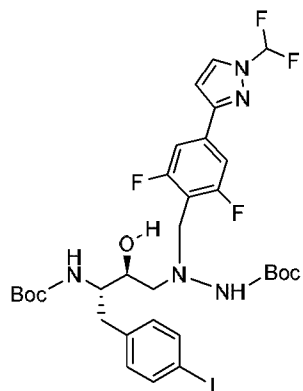
with Compound P4:



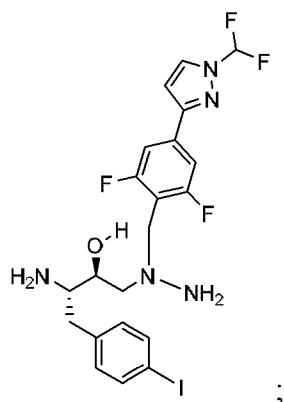
to provide a compound of structure:



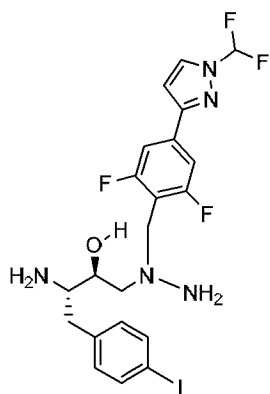
b) deprotecting a compound of structure:



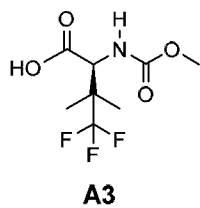
with HCl to provide a compound of structure:



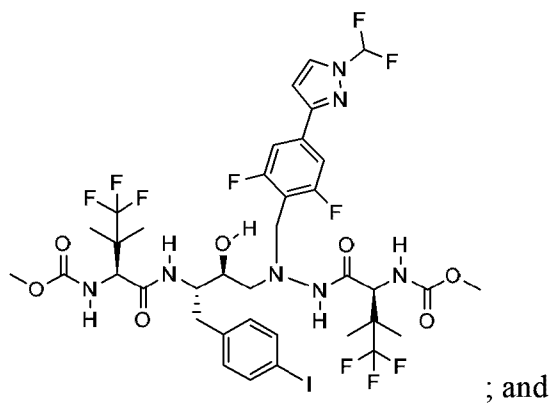
c) reacting a compound of structure:



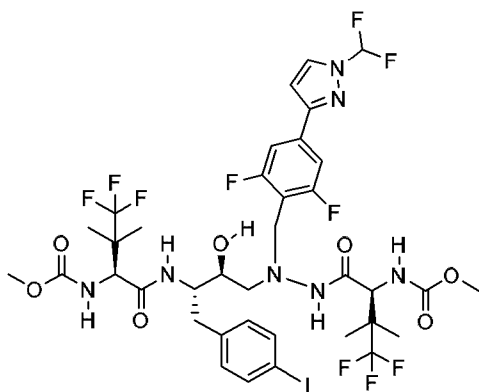
with Compound A3:



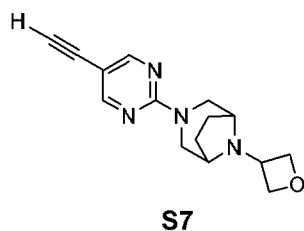
to provide a compound of structure:



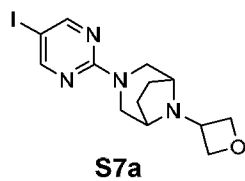
d) reacting a compound of structure:



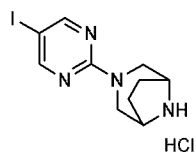
with Compound S7:



78. The process of claim 77, wherein Compound S7 is prepared by a process comprising reacting trimethylsilylacetylene (TMSA) with Compound S7a:

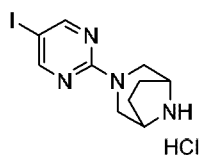


79. The process of claim 78, wherein Compound S7a is prepared by a process comprising reacting oxetan-3-one with a compound of structure:



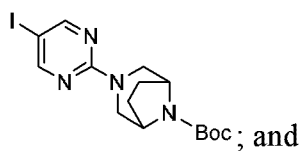
in the presence of sodium cyanoborohydride.

80. The process of claim 79, wherein the compound of structure:

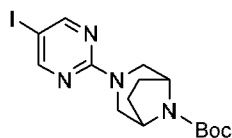


is prepared by a process comprising:

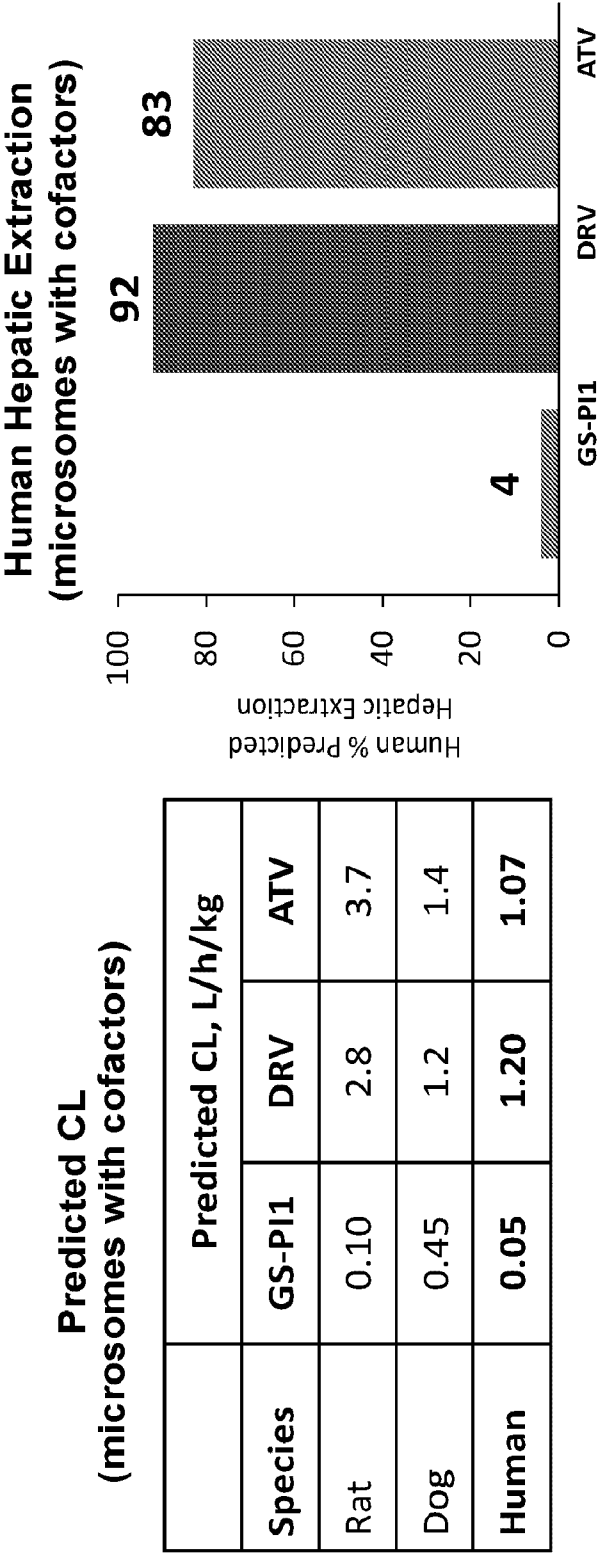
a) reacting *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate with 2-chloro-5-iodopyrimidine to provide a compound of structure:



b) deprotecting a compound of structure:



with HCl.



Intravenous Pharmacokinetics of GS-PI1, DRV, and ATV

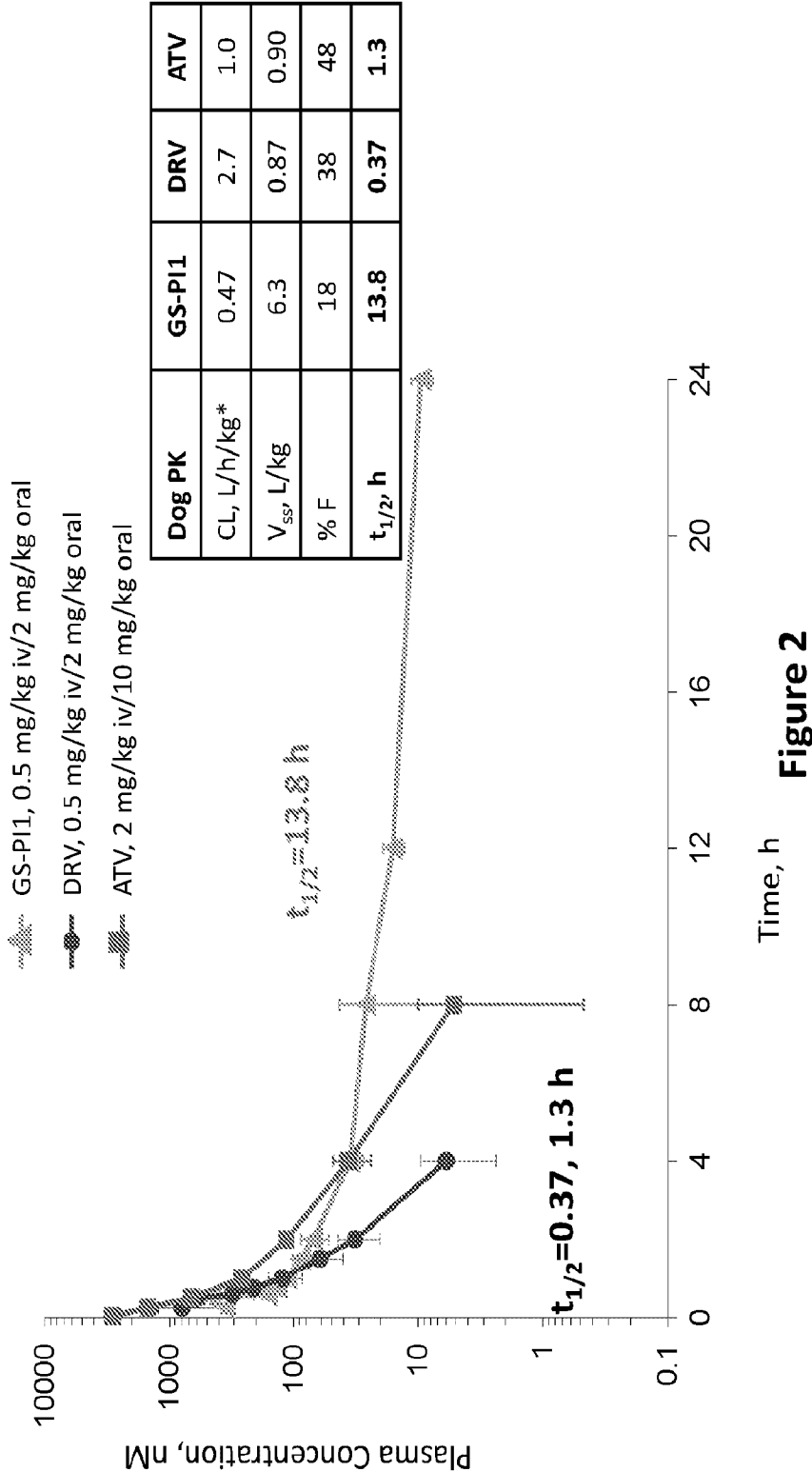


Figure 2

Intravenous Pharmacokinetics of GS-PI1,
DRV, and ATV

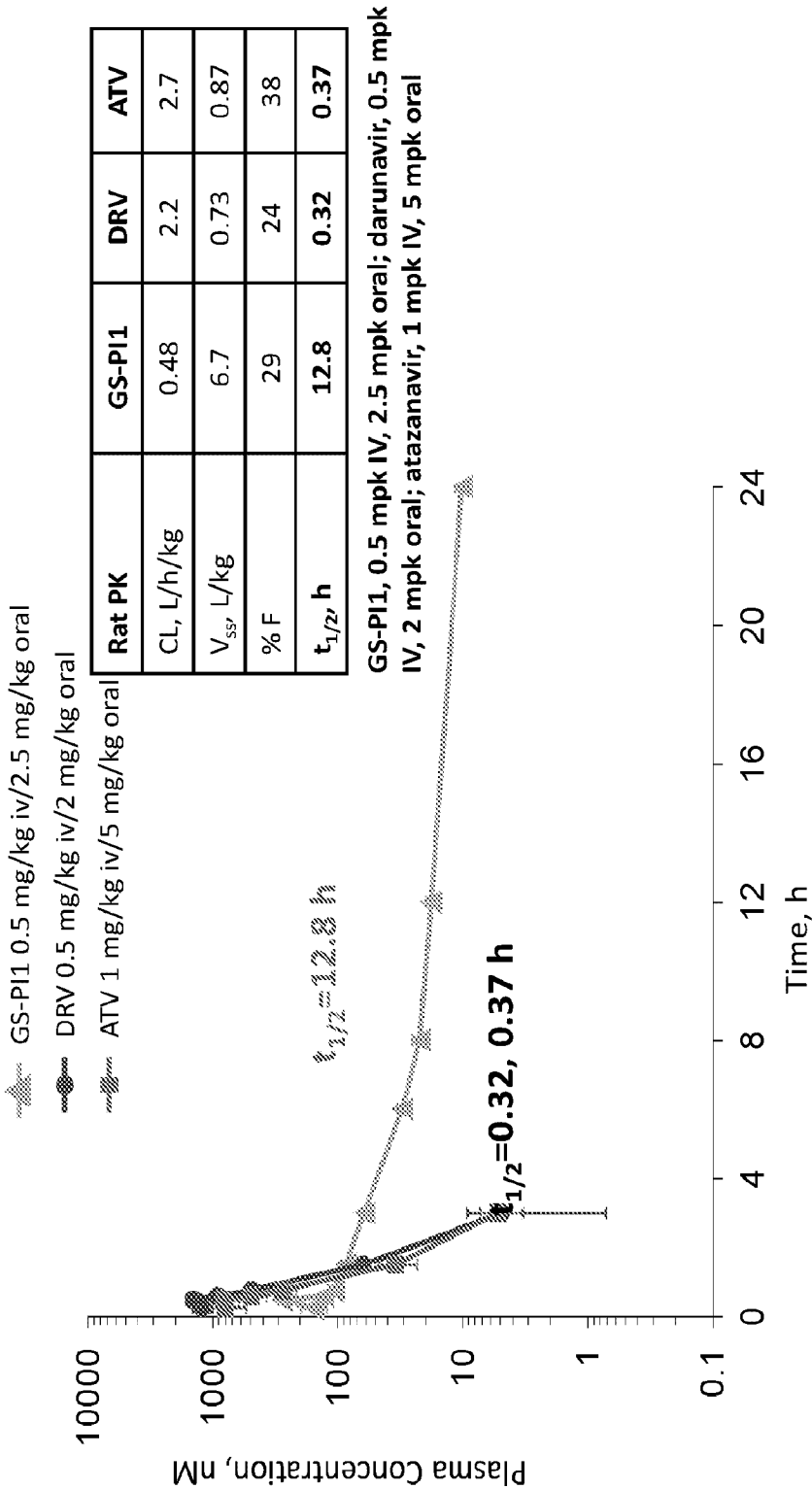
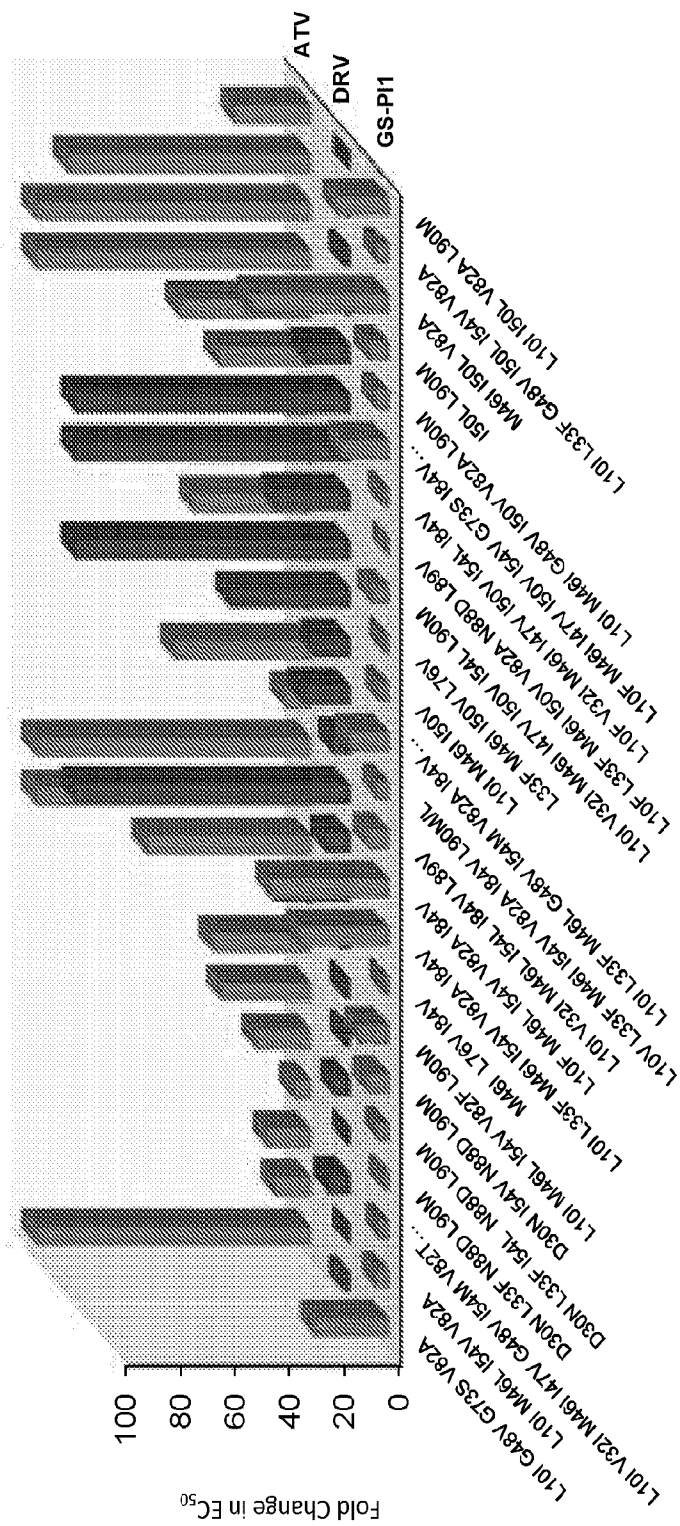


Figure 3

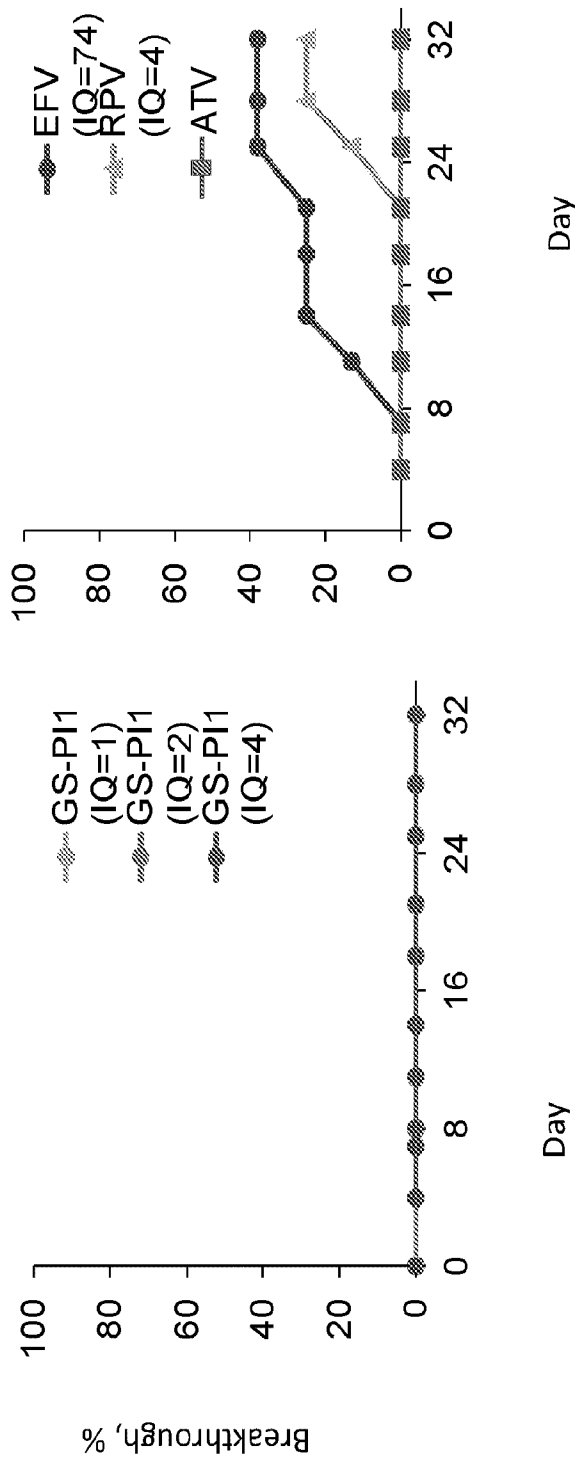
Fold Change vs Wild Type for Clinically Relevant RAMs



Mutant Virus

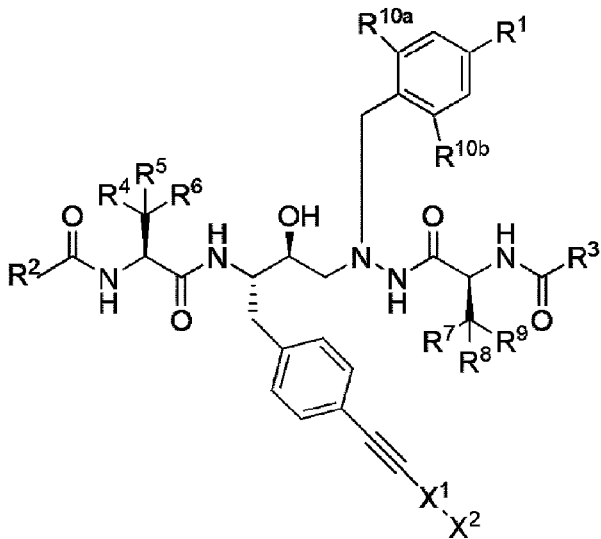
Figure 4

Resistance Breakthrough Assay



- GS-PI1 does not breakthrough at IQ of 1
- EFV and RPV breakthrough at their clinical IQ; ATV does not

Figure 5



(Ia)